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Ambient Water Quality Criteria: DDT

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DDT

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for DDT. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no re, ...

KEYWORDS: *Water quality, *Toxicology, *DDT, *Toxic substances, *Water pollution effects(Humans).

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CRITERION DOCUMENT

DDT AND METABOLITES

CRITERIA

Aquatic Life

For DDT and metabolites the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.00023 µg/l as a 24-hour average and the concentration should not exceed 0.41 µg/l at any time.

The data base for saltwater aquatic life is insufficient to allow use of the Guidelines. The following recommendation is inferred from toxicity data for freshwater organisms.

For DDT and metabolites the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 0.0067 µgl as a 24-hour average and the concentration should not exceed 0.021 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to DDT through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of DDT estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim targe risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.98 ng/l, 0.098 ng/l, and .0098 ng/l, respectively. If water alone is consumed, the water concentration should be less than 0.36 µg/l to keep the lifetime cancer risk below 10^{-5}.

Introduction

DDT, first synthesized in Germany in 1874, has been used extensively world-wide for public health and agricultural programs. Its efficacy as a broad spectrum insecticide and its low cost continue to make it the insecticide of choice for those measures for most of the world.

Following an extensive review of health and environmental hazards of the use of DDT, U.S. EPA decided to ban further use of DDT. This decision was based on several properties of DDT that had been well evidenced; (1) DDT and its metabolites are toxicants with long-term persistence in soil and water, (2) it is widely dispersed by erosion, runoff and volatilization, (3) the low-water solubility and high lipophilicity of DDT result in concentrated accumulation of DDT in the fat of wildlife and humans which may be hazardous. Agricultural use of DDT was canceled by the U.S. EPA in December, 1972. Prior to this, DDT had been widely used in the U.S. with a peak usage in 1959 of 80 million pounds. This amount decreased steadily to less than 12 million pounds by 1972. Since the 1972 ban, the use of DDT in the U.S. has been effectively discontinued.

DDT is acutely toxic to freshwater fishes at concentrations as low as 0.8 µg/l (Marking, 1966) and to invertebrates at 0.18 µg/l (Sanders, 1972). It is chronically toxic to the fathead minnow in the range of 0.37 to 1.48 µg/l (Jarvinen, et al. 1977). An average bioconcentration factor of 640,000 was calculated using data on 26 species of fish. For saltwater fishes concentrations of DDT as low as 0.2 µg/l have been

reported to be acutely toxic (Eisler, 1970). For invertebrates the figure is 0.14 µg/l (Schimmel and Patrick, 1975). Chronic toxicity data for saltwater organisms were not available. The average marine fish bioconcentration factor was found to be 22,467. Criteria for both freshwater and marine organisms are based on bioconcentration.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

DDT is an insecticide that has been in use for many years and has probably been subject to more investigations than the other chlorinated hydrocarbon pesticides such as aldrin, dieldrin, endrin, chlordane, and toxaphene.

In regard to fish toxicity, DDT has an intermediate toxicity when compared with other chlorinated hydrocarbon pesticides. It is less toxic than aldrin, dieldrin, endrin, and toxaphene but more toxic than chlordane, heptachlor, lindane, and methoxychlor (Henderson, et al. 1959; Katz, 1961).

Most acute data are from static tests; few flow-through studies have been conducted. Chronic test data are available for only one species of fish and none are available for aquatic invertebrates.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Few data are available on freshwater plant effects and those that are indicate a wide range in concentrations where effects occur.

Many references on bioconcentration data are available, however, a number of these were not usable, either because the organisms did not appear to reach an equilibrium with the water concentration in laboratory experiments, or in the case of field monitoring, there was not adequate documentation of the water concentration.

Acute Toxicity

Acute toxicity data are available for 25 species of fish for a total of 111 values (Table 1); of these, only four values are not 96-hours in duration. Three of the 111 LC50 values are from flow-through tests, and the rest are from static tests. Only one of the three flow-through tests has a measured water concentration. The flow-through LC50 value for rainbow trout fry (Tooby, et al. 1975) is equal to or less than 85 percent of the 13 static values for the same species. The flow-through LC50 value for brown trout (Alabaster, 1969) is less than 50 percent of the other three values for the same species. The only flow-through test with a measured water concentration (Jarvinen, et al. 1977) is for the fathead minnow, and the LC50 value is greater than 87 percent of all static LC50 values for the same species. Since the water solubility of DDT is not high, it could be assumed that static tests would underestimate toxicity as indicated by the rainbow trout and brown trout data. The fathead minnow data, however, are in contrast with these, perhaps because of species variability. Lincer, et al. (1970) demonstrated that the fathead minnow was more sensitive to DDT in the static than in the flow-through test (48-hour static = 7.4 μg/l; 48-hour flow-through = > 40 μg/l) and Macek and Sanders (1970) determined that among the five fish species tested, variation in susceptibility to DDT was greatest in the fathead minnow. Interspecific variability, shown by the LC50 values in Table 1, indicates that the fathead minnow is more variable than 87 percent of the 25 species for which there are data available. Only three species are more variable, the goldfish, guppy, and the brook trout; of these, the goldfish is the most variable. The yellow perch is the most sensitive fish species to DDT (96-hour LC50 of 0.6 μg/l; Marking, 1966) whereas the least sensitive species is the goldfish (96-hour LC50 of 180 μg/l; Marking, 1966). Therefore, the range of species sensitivity is 300 times.

Sixty percent of the species in Table 1 have at least one LC50 value below the geometric mean for all species, but if based upon the total number of data points, only 32 percent of all individual LC50 values fall below this mean. When the geometric mean of all species in Table 1 is divided by the sensitivity factor (3.9), the LC50 value calculated to be equal to or less than the LC50 value for 95 percent of all species is 1.3 μg/l. This value is higher than only five values in the table, which are less than five percent of the total number of values given, suggesting a good fit of the data to the procedures in the Guidelines. The Final Fish Acute Value is 1.3 μg/l.

Data are available for 19 invertebrate species for a total of 50 data points (Table 2). Invertebrate species for the most part are more sensitive than fish, but the range in species sensitivity is greater (10,000 times as compared to 300 times for fish). The least sensitive invertebrate species is the stonefly, Pteronarcys californica for which a 96-hour LC50 value of 1,800 µg/l was demonstrated by Gaufin, et al. (1965). This LC50 value is almost five times greater than the arithmetic mean of the other three LC50 values for the same species (Table 2). The most sensitive aquatic invertebrate species is the one week-old crayfish, Orconectes nais (LC50 = 0.18 µg/l; Sanders, 1972).

Only two of the data for invertebrate species (Table 2) were derived from flow-through tests. None of the data have measured water concentrations. Seventy percent of all data points are from 96-hour tests, 28 percent from 48-hour tests, and only two percent or one data point from a 26-hour test that was used as a 24-hour value. The result of one flow-through test in Table 2 is one-fourth of the static test result for the same species of scud, Gammarus fasciatus (Sanders, 1972) whereas in another comparison the result of a static test is lower than the result from a flow-through test with the glass shrimp, Palaemonetes kadiakensis, (Sanders, 1972). Therefore, as with the fish acute data, species variability is demonstrated in toxicity differences between static and flow-through tests. In Table 2, TDE is more toxic than DDT to three invertebrate species (a glass shrimp, Palaemonetes kadiakensis and two species of scud, Gammarus fasciatus and Gammarus lacustris but less toxic than DDT to the cladocerans, Daphnia pulex and Simocephalus serrulatus and the sowbug, Asellus brevicaudus.

When the geometric mean of all the data points in Table 2 is divided by the species sensitivity factor (21), the estimated value at or below the LC50 value for 95 percent of all species is 0.41 µg/l. This value is lower than 90 percent of all the LC50 values and lower than the LC50 values for 89.5 percent of all of the species in Table 2. When compared to the geometric mean of the adjusted LC50 value for each species, it is lower than that of all of the 19 species in the table. Because of the variability in the invertebrate data base, the use of the sensitivity factor seems to be appropriate. Since the Final Invertebrate Acute Value (0.41; Table 2) is lower than the Final Fish Acute Value (1.3 µg/l; Table 1), the Final Acute Value for freshwater aquatic life is 0.41 µg/l.

Chronic Toxicity

One chronic test with fathead minnows was found (Table 3). The comparable 96-hour LC50 value (Jarvinen, et al. 1977) indicates that the acute toxicity value is 65 times higher than the chronic toxicity value. When the chronic value is divided by the species sensitivity factor (6.7), a value (0.11 µg/l) is obtained which should protect 95 percent of all species. Another method of estimating the same value is obtained by multiplying the Final Fish Acute Value by the application factor calculated from the fathead minnow data; this estimate is 0.12 µg/l, only 10 percent higher. There is no indication of the range of species sensitivity for chronic toxicity since only one chronic value is available. Since fathead minnows are among the least sensitive of the species tested (Table 1; 79 percent of all species are more sensitive), reduction of the chronic fathead minnow data by the sensitivity factor is reasonable to protect more sensitive species from chronic toxicity. The Final Fish Chronic Value is the lowest of the three estimates in Table 3, or 0.11 µg/l.

No invertebrate chronic toxicity data were found.

Plant Effects

Four species of algae have a wide range of sensitivity (2,700 times) with the highest about equally sensitive to DDT as fish and invertebrate species (Table 4). The lowest and Final Plant Value is 0.30 µg/l, determined from the growth and morphology data for Chlorella sp. (Sodergren, 1968).

Residues

An average bioconcentration factor of 640,000 was calculated for the 31 data points on the 26 species of fish in Table 5. Because of the persistence of DDT and its ability to bioaccumulate, field data were included if adequate water concentration measurements were provided. Twenty-two field generated data points for 20 species of fish are available (Table 5) with an arithmetic mean bioconcentration of 842,822, whereas only nine laboratory data points for nine species of fish are available with an arithmetric mean bioconcentration of 125,976. This indicates an almost seven times greater bioconcentration in the field than in laboratory tests, which may be due to the many additional trophic levels involved in field exposures or a difference in lipid content.

Data points in Table 5 pertaining to maximum permissible tissue concentrations indicate that long-term dietary dosage at 2.8 to 3 mg/kg DDE (wet weight) can have adverse effects on reproduction of mallards (Heath, et al. 1969; Haseltine, et al. 1974), black ducks (Longcore, et al. 1971; Longcore and Stendell, 1977), and screech owls (McLane and Hall, 1972). DDE has been found to constitute 50 to 90 percent of the DDT analogs present in fish (Jarvinen, et al. 1977). The DDE no-effect concentration for shell thinning was estimated to be 0.5 mg/kg or less in eggs of brown pelicans (Blus, et al. 1972). Many times higher concentrations in the eggs than concentrations that were fed for several months have been found for other species. Ten times higher concentrations were observed in black duck eggs (Longcore, et al. 1971; Longcore and Stendell, 1977) and almost eight times higher in sparrow hawk eggs (Lincer, 1975). Therefore, a dietary dosage as low as 0.1 mg/kg in brown pelicans, which might be accumulated to over 0.5 mg/kg in the eggs, might not protect them from shell thinning. Anderson, et al. (1975) found that although the major food source of brown pelicans contains a residue concentration of only 0.15 mg/kg the pelican numbers were still below that necessary for population stability. Therefore, the residue concentration of 0.15 mg/kg divided by the bioconcentration factor of 640,000 gives a Residue Limited Toxicant Concentration (RLTC) of 0.00023 µg/l.

Of the three available values, the Final Fish Chronic Value (0.11 µg/l), the Final Plant Value (0.30 µg/l), and the RLTC (0.00023 µg/l), the RLTC is the lowest and thus 0.00023 µg/l becomes the Final Chronic Value.

Miscellaneous

Table 6 contains additional data points concerning the effect of DDT on 23 species of freshwater aquatic life. None of these data values however, is lower than the selected Final Chronic

Value (0.00023 µg/l). The values range from extended time LC50 values to physiological and behavioral effects. The lowest value in Table 6 is a hyperactive locomotor response observed by Ellgaard, et al. (1977) for the bluegill, exposed at 0.008 µg/l. This value is almost 35 times higher than the Final Chronic Value.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 1.3 µg/l

Final Invertebrate Acute Value = 0.41 µg/l

Final Acute Value = 0.41 µg/l

Final Fish Chronic Value = 0.11 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 0.30 µg/l

Residue Limited Toxicant Concentration = 0.00023 µg/l

Final Chronic Value = 0.00023 µg/l

0.44 x Final Acute Value = 0.18 µg/l

The maximum concentration of DDT and metabolites is the Final Acute Value of 0.41 µg/l and the 24-hour average concentration is the Final Chronic Value of 0.00023 µg/l. No importnt adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For DDT and metabolites the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.00023 µg/l as a 24-hour average and the concentration should not exceed 0.41 µg/l at any time.

Table 1. Freshwater fish acute values for DDT and metabolites

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Coho salmon, Oncorhynchus kisutch	S	U	DDT	96	44	24.05	Katz, 1961
Coho salmon, Oncorhynchus kisutch	S	U	DDT	96	4	2.19	Macek & McAllister, 1970
Coho salmon, Oncorhynchus kisutch	S	U	DDT	96	11.3	6.18	Post & Schroeder, 1971
Coho salmon, Oncorhynchus kisutch	S	U	DDT	96	18.5	10.11	Post & Schroeder, 1971
Coho salmon, Oncorhynchus kisutch	S	U	DDT	96	13	7.11	Schaumburg, et al. 1967
Chinook salmon, Oncorhynchus tshawytscha	S	U	DDT	96	11.5	6.29	Katz, 1961
Cutthroat trout, Salmo clarki	S	U	DDT	96	0.85	0.46	Post & Schroeder, 1971
Cutthroat trout, Salmo clarki	S	U	DDT	96	1.37	0.75	Post & Schroeder, 1971
Rainbow trout, Salmo gairdneri	S	U	DDT	96	42	22.96	Katz, 1961
Rainbow trout, Salmo gairdneri	S	U	DDT	96	7	3.83	Macek & McAllister, 1970
Rainbow trout, Salmo gairdneri	S	U	DDT	96	7.2	3.94	Macek & Sanders, 1970
Rainbow trout, Salmo gairdneri	S	U	DDT	96	14	7.65	Marking, 1966
Rainbow trout, Salmo gairdneri	S	U	DDT	96	4.6	2.51	Marking, 1966

Table 1. (Continued)

Organism	Bioassay Method *	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, *Salmo gairdneri*	S	U	DDT	96	7.2	3.94	Marking, 1966
Rainbow trout, *Salmo gairdneri*	S	U	DDT	96	15	8.20	Marking, 1966
Rainbow trout, *Salmo gairdneri*	S	U	DDT	96	17	9.29	Marking, 1966
Rainbow trout, *Salmo gairdneri*	S	U	DDT	96	13	7.11	Marking, 1966
Rainbow trout, *Salmo gairdneri*	S	U	DDT	96	12	6.56	Marking, 1966
Rainbow trout, *Salmo gairdneri*	S	U	DDT	96	2.4	1.31	Marking, 1966
Rainbow trout, *Salmo gairdneri*	S	U	DDT	96	1.7	0.93	Post & Schroeder, 1971
Rainbow trout (fry), *Salmo gairdneri*	FT	U	DDT	96	2.4	1.85	Tooby, et al. 1975
Brown trout (alevin), *Salmo trutta*	FT	U	DDT	48	2.5	1.56	Alabaster, 1969
Brown trout (fingerling), *Salmo trutta*	S	U	DDT	96	17.5	9.57	King, 1962
Brown trout, *Salmo trutta*	S	U	DDT	96	2	1.09	Macek & McAllister, 1970
Brown trout, *Salmo trutta*	S	U	DDT	96	10.9	5.96	Marking, 1966
Brook trout, *Salvelinus fontinalis*	S	U	DDT	96	7.2	3.94	Marking, 1966
Brook trout, *Salvelinus fontinalis*	S	U	DDT	96	17	9.29	Marking, 1966
Brook trout, *Salvelinus fontinalis*	S	U	DDT	96	20	10.93	Marking, 1966

Table 1. (Continued)

Organism	Bioassay Method *	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Brook trout, *Salvelinus fontinalis*	S	U	DDT	96	1.8	0.98	Marking, 1966
Brook trout, *Salvelinus fontinalis*	S	U	DDT	24	54	19.48	Miller & Ogilvie, 1975
Brook trout, *Salvelinus fontinalis*	S	U	DDT	96	7.4	4.05	Post & Schroeder, 1971
Brook trout, *Salvelinus fontinalis*	S	U	DDT	96	11.9	6.51	Post & Schroeder, 1971
Lake trout, *Salvelinus namaycush*	S	U	DDT	96	9.1	4.97	Marking, 1966
Lake trout, *Salvelinus namaycush*	S	U	DDT	96	9.5	5.19	Marking, 1966
Northern pike, *Esox lucius*	S	U	DDT	96	1.7	0.93	Marking, 1966
Goldfish, *Carassius auratus*	S	U	DDT	96	21	11.48	Macek & McAllister, 1970
Goldfish, *Carassius auratus*	S	U	DDT	96	76	41.55	Marking, 1966
Goldfish, *Carassius auratus*	S	U	DDT	96	27	14.76	Marking, 1966
Goldfish, *Carassius auratus*	S	U	DDT	96	32	17.49	Marking, 1966
Goldfish, *Carassius auratus*	S	U	DDT	96	180	98.41	Marking, 1966
Goldfish, *Carassius auratus*	S	U	DDT	96	40	21.87	Marking, 1966
Goldfish, *Carassius auratus*	S	U	DDT	96	35	19.13	Marking, 1966
Goldfish, *Carassius auratus*	S	U	DDT	96	21	11.48	Marking, 1966

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Goldfish, Carassius auratus	S	U	DDT	96	36	19.68	Henderson, et al. 1959
Northern redbelly dace, Chrosomus eos	S	U	DDT	96	68	37.18	Marking, 1966
Carp, Cyprinus carpio	S	U	DDT	96	10	5.47	Macek & McAllister, 1970
Carp, Cyprinus carpio	S	U	DDT	96	9.2	5.03	Marking, 1966
Carp, Cyprinus carpio	S	U	DDT	96	4.0	2.19	Marking, 1966
Carp, Cyprinus carpio	S	U	DDT	96	11.3	6.18	Marking, 1966
Carp, Cyprinus carpio	S	U	DDT	96	12	6.56	Marking, 1966
Carp, Cyprinus carpio	S	U	DDT	96	6.9	3.77	Marking, 1966
Carp, Cyprinus carpio	S	U	DDT	96	6	3.28	Marking, 1966
Fathead minnow, Pimephales promelas	FT	M	DDT	96	48	48	Jarvinen, et al. 1977
Fathead minnow, Pimephales promelas	S	U	DDT	48	7.4	3.28	Lincer, et al. 1970
Fathead minnow, Pimephales promelas	S	U	DDT	96	19	10.39	Macek & McAllister, 1970
Fathead minnow, Pimephales promelas	S	U	DDT	96	19.9	10.88	Macek & Sanders, 1970
Fathead minnow, Pimephales promelas	S	U	DDT	96	58	31.71	Priester, 1965
Fathead minnow, Pimephales promelas	S	U	DDT	96	42	22.96	Henderson, et al. 1959

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, Pimephales promelas	S	U	DDT	96	45	24.60	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	DDT	96	26	14.21	Henderson, et al. 1959
Fathead minnow, Pimephales promelas	S	U	DDT	96	26	14.21	Henderson, et al. 1959
Black bullhead, Ictalurus melas	S	U	DDT	96	5	2.73	Macek & McAllister, 1970
Black bullhead, Ictalurus melas	S	U	DDT	96	42	22.96	Marking, 1966
Black bullhead, Ictalurus melas	S	U	DDT	96	23.5	12.85	Marking, 1966
Black bullhead, Ictalurus melas	S	U	DDT	96	17	9.29	Marking, 1966
Black bullhead, Ictalurus melas	S	U	DDT	96	20	10.93	Marking, 1966
Channel catfish, Ictalurus punctatus	S	U	DDT	96	16	8.75	Macek & McAllister, 1970
Channel catfish, Ictalurus punctatus	S	U	DDT	96	17.4	9.51	Macek & Sanders, 1970
Channel catfish, Ictalurus punctatus	S	U	DDT	96	17.5	9.57	Marking, 1966
Channel catfish, Ictalurus punctatus	S	U	DDT	96	17.5	9.57	Marking, 1966
Mosquitofish, Gambusia affinis	S	U	DDT	48	43	19.04	Dziuk & Plapp, 1973
Guppy, Lebistes reticulatus	S	U	DDT	96	19.5	10.66	King, 1962
Guppy, Lebistes reticulatus	S	U	DDT	96	56	30.62	Henderson, et al. 1959

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Brook stickleback, Eucalia inconstans	S	U	DDT	96	67	36.63	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	2.8	1.53	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	3	1.64	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	3.9	2.13	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	6.7	3.66	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	6.4	3.50	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	4.4	2.41	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	3.6	1.97	Marking, 1966
Green sunfish, Lepomis cyanellus	S	U	DDT	96	5	2.73	Marking, 1966
Pumpkinseed, Lepomis gibbosus	S	U	DDT	96	7.5	4.10	Marking, 1966
Pumpkinseed, Lepomis gibbosus	S	U	DDT	96	6.7	3.66	Marking, 1966
Pumpkinseed, Lepomis gibbosus	S	U	DDT	96	2.8	1.53	Marking, 1966
Pumpkinseed, Lepomis gibbosus	S	U	DDT	96	3.6	1.97	Marking, 1966
Pumpkinseed, Lepomis gibbosus	S	U	DDT	96	1.8	0.98	Marking, 1966
Bluegill, Lepomis macrochirus	S	U	DDT	96	8	4.37	Macek & McAllister, 1970

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	9.5	5.19	Macek & Sanders, 1970
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	4.3	2.35	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	3.6	1.97	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	1.7	0.93	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	1.2	0.66	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	3	1.64	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	4.6	2.51	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	7	3.83	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	9.4	5.14	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	7	3.83	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	2.8	1.53	Marking, 1966
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	21	11.48	Henderson, et al. 1959
Bluegill, *Lepomis macrochirus*	S	U	DDT	96	4.9	2.68	Marking, 1966
Longear sunfish, *Lepomis megalotis*	S	U	DDT	96	12.5	6.83	Marking, 1966
Longear sunfish, *Lepomis megalotis*	S	U	DDT	96	5	2.73	Macek & McAllister, 1970
Redear sunfish, *Lepomis microlophus*							

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Largemouth bass, *Micropterus salmoides*	S	U	DDT	96	2	1.09	Macek & McAllister, 1970
Largemouth bass, *Micropterus salmoides*	S	U	DDT	96	1.8	0.98	Macek & Sanders, 1970
Largemouth bass, *Micropterus salmoides*	S	U	DDT	96	0.8	0.44	Marking, 1966
Yellow perch, *Perca flavescens*	S	U	DDT	96	9	4.92	Macek & McAllister, 1970
Yellow perch, *Perca flavescens*	S	U	DDT	96	0.8	0.44	Marking, 1966
Yellow perch, *Perca flavescens*	S	U	DDT	96	0.6	0.33	Marking, 1966
Yellow perch, *Perca flavescens*	S	U	DDT	96	1.5	0.82	Marking, 1966
Freshwater drum, *Aplodinotus grunniens*	S	U	DDT	96	10	5.47	Marking, 1966

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 5.05 µg/l $\frac{5.05}{3.9} = 1.3$ µg/l

Lowest value from a flow-through test with measured concentrations = 48 µg/l

Table 2. Freshwater invertebrate acute values for DDT and metabolites

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, Daphnia magna	S	U	DDT	26	5.5	4.66	Crosby, et al. 1966
Cladoceran, Daphnia magna	S	U	DDT	48	4	3.39	Macek & Sanders, 1970
Cladoceran, Daphnia magna	S	U	DDT	48	1.48	1.25	Priester, 1965
Cladoceran, Daphnia pulex	S	U	DDT	48	0.36	0.30	Sanders & Cope, 1966
Cladoceran, Daphnia pulex	S	U	TDE	48	3.2	2.71	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S	U	DDT	48	2.5	2.12	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S	U	DDT	48	2.8	2.37	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S	U	TDE	48	4.5	3.81	Sanders & Cope, 1966
Cladoceran, Simocephalus serrulatus	S	U	TDE	48	5.2	4.40	Sanders & Cope, 1966
Sowbug, Asellus brevicaudus	S	U	DDT	48	4.7	1.71	Macek & Sanders, 1970
Sowbug, Asellus brevicaudus	S	U	DDT	96	4	3.39	Sanders, 1972
Sowbug, Asellus brevicaudus	S	U	TDE	96	10	8.47	Sanders, 1972
Scud, Gammarus fasciatus	S	U	DDT	48	3.6	1.31	Macek & Sanders, 1970
Scud, Gammarus fasciatus	S	U	DDT	96	3.2	2.71	Sanders, 1972
Scud, Gammarus fasciatus	FT	U	DDT	96	0.8	0.62	Sanders, 1972

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Scud, *Gammarus fasciatus*	S	U	DDT	96	1.8	1.52	Sanders, 1972
Scud, *Gammarus fasciatus*	S	U	TDE	96	0.6	0.51	Sanders, 1972
Scud, *Gammarus fasciatus*	S	U	TDE	96	0.86	0.73	Sanders, 1972
Scud, *Gammarus lacustris*	S	U	DDT	96	9	7.62	Gaufin, et al. 1965
Scud, *Gammarus lacustris*	S	U	DDT	96	1	0.85	Sanders, 1969
Scud, *Gammarus lacustris*	S	U	TDE	96	0.64	0.54	Sanders, 1969
Seed shrimp, *Cypridopsis vidua*	S	U	DDT	48	54	19.67	Macek & Sanders, 1970
Glass shrimp, *Palaemonetes kadiakensis*	S	U	DDT	48	4.2	1.53	Macek & Sanders, 1970
Glass shrimp, *Palaemonetes kadiakensis*	S	U	DDT	96	2.3	1.95	Sanders, 1972
Glass shrimp, *Palaemonetes kadiakensis*	FT	U	DDT	96	3.5	2.70	Sanders, 1972
Glass shrimp, *Palaemonetes kadiakensis*	S	U	TDE	96	0.68	0.58	Sanders, 1972
Crayfish, *Orconectes nais*	S	U	DDT	96	100	84.70	Sanders, 1972
Crayfish (1-day-old), *Orconectes nais*	S	U	DDT	96	0.30	0.25	Sanders, 1972
Crayfish (1-wk-old), *Orconectes nais*	S	U	DDT	96	0.18	0.15	Sanders, 1972
Crayfish (2-wk-old), *Orconectes nais*	S	U	DDT	96	0.20	0.17	Sanders, 1972

Table 2. (Continued)

Organism	Bioassay Method	Test Conc.	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Crayfish (3-wk-old), Orconectes nais	S	U	DDT	96	0.24	0.20	Sanders, 1972
Crayfish (5-wk-old), Orconectes nais	S	U	DDT	96	0.90	0.76	Sanders, 1972
Crayfish (8-wk-old), Orconectes nais	S	U	DDT	96	28	23.72	Sanders, 1972
Crayfish (10-wk-old), Orconectes nais	S	U	DDT	96	30	25.41	Sanders, 1972
Crayfish, Procambarus acutus	S	U	DDT	48	[illegible]	1.09	Albaugh, 1972
Mayfly, Ephemerella grandis	S	U	DDT	96	25	21.18	Gaufin, et al. 1965
Stonefly, Acroneuria pacifica	S	U	DDT	96	410	347.27	Gaufin, et al. 1961
Stonefly, Acroneuria pacifica	S	U	DDT	96	320	271.04	Gaufin, et al. 1965
Stonefly, Claassenia sabulosa	S	U	DDT	96	3.5	2.96	Sanders & Cope, 1968
Stonefly, Pteronarcella badia	S	U	DDT	96	1.9	1.61	Sanders & Cope, 1968
Stonefly, Pteronarcys californica	S	U	DDT	96	1,800	1,524.60	Gaufin, et al. 1965
Stonefly, Pteronarcys californica	S	U	DDT	96	7	5.93	Sanders & Cope, 1968
Stonefly, Pteronarcys californica	S	U	TDE	96	380	321.86	Sanders & Cope, 1968
Stonefly, Pteronarcys californica	S	U	DDT	96	560	474.32	Gaufin, et al. 1961
Damselfly, Ischnura verticalis	S	U	DDT	48	22.5	8.19	Macek & Sanders, 1970

Table 2. (Continued)

Organism	Bioassay Method	Test Conc.	Chemical Description	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Caddisfly, *Arctopsyche grandis*	S	U	DDT	96	175	148.23	Gaufin, et al. 1965
Caddisfly, *Hydropsyche californica*	S	U	DDT	96	48	40.66	Gaufin, et al. 1965
Planarian, *Polycelis felina*	S	U	DDT	96	1,230	1,041.81	Kouyoumjian & Uglow, 1974
Planarian, *Polycelis felina*	S	U	DDE	96	1,050	889.35	Kouyoumjian & Uglow, 1974
Planarian, *Polycelis felina*	S	U	TDE	96	740	626.78	Kouyoumjian & Uglow, 1974

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* S = static, FT = flow-through

** U = unmeasured

Geometric mean of adjusted values = 8.57 µg/l $\frac{8.57}{21}$ = 0.41 µg/l

Table 3. Freshwater fish chronic values for DDT and metabolites (Jarvinen, et al. 1977)

Organism	**Test***	**Limits (µg/l)**	**Chronic Value (µg/l)**
Fathead minnow, *Pimephales promelas*	LC	0.37-1.48	0.74

* LC = life cycle or partial life cycle

Geometric mean of chronic values = 0.74 µg/l $\frac{0.74}{6.7}$ = 0.11 µg/l

Lowest chronic value = 0.74 µg/l

Application Factor Values

Species	**96-hr LC50 (µg/l)**	**MATC (µg/l)**	**AF**
Fathead minnow, *Pimephales promelas*	48	0.74	0.015

Geometric mean LC50 = 48 µg/l

Geometric mean AF = 0.015

$0.015 \sqrt{48 \text{ µg/l} \times 1.3 \text{ µg/l}} = 0.12$ µg/l

Table 4. Freshwater plant effects for DDT and metabolites

Organism	Effect	Concentration (µg/l)	Reference
Alga, *Anacystis nidulans*	Growth	800	Batterton, et al. 1972
Alga, *Chlorella* sp.	Growth & morphology	0.3	Sodergren, 1968
Alga, *Scenedesmus quadricaudata*	Growth	100	Stadnyk, et al. 1971
Alga, *Selanastrum capricornutum*	Photosynthesis	3.6	Lee, et al. 1976

Lowest plant value = 0.3 µg/l

Table 5. Freshwater residues for DDT and metabolites

Organism	Bioconcentration Factor	Time (days)	Reference
Coontail, *Ceratophyllum demersum*	1,950	30	Eberhardt, et al. 1971
Cladophora, *Cladophora* sp.	21,580	30	Eberhardt, et al. 1971
Duckweed, *Lemna minor*	1,210	30	Eberhardt, et al. 1971
Water milfoil, *Myriophyllum* sp.	1,870	30	Eberhardt, et al. 1971
Curly leaf pondweed, *Potamogeton cripus*	14,280	30	Eberhardt, et al. 1971
Narrow-leaf pondweed, *Potamogeton foliosus*	781	30	Eberhardt, et al. 1971
Sago pondweed, *Potamogeton pectinatus*	6,360	30	Eberhardt, et al. 1971
Soft stem bulrush, *Scirpus validus*	495	30	Eberhardt, et al. 1971
Bur reed, *Sparganium eurycarpum*	623	30	Eberhardt, et al. 1971
Bladderwort, *Utricularia vulgaris*	2,200	30	Eberhardt, et al. 1971
Mussel, *Anodonta grandis*	2,400	21	Bedford & Zabik, 1973
Clams (five species composite), *Lampsilis siliquoidea* *Lampsilis ventricosa* *Lasmigona costata* *Fusconaia flava* *Ligumia recta*	12,500	56	Jarvinen, et al. 1977
Cladoceran, *Daphnia magna*	9,923*	14	Priester, 1965
Zooplankton (mixed), *Daphnia* sp. *Keratella* sp.	63,500	21	Hamelink & Waybrant, 1976

Table 5. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Freshwater prawn, Palaemonetes paludosus	7,000	field	Kolipinski, et al. 1971
Crayfish, Orconectes punctata	5,060	30	Eberhardt, et al. 1971
Crayfish, Procambarus alleni	1,947	field	Kolipinski, et al. 1971
Mayfly (nymph), Ephemera danica	4,075	5	Sodergren & Svensson, 1973
Dragonfly (nymph), Tetragoneuria sp.	2,700	20	Wilkes & Weiss, 1971
Bloodworm, Tendipes sp.	4,750	30	Eberhardt, et al. 1971
Red leech, Erpobdella punctata	7,520	30	Eberhardt, et al. 1971
Alewife, Alosa pseudoharengus	1,296,666	field	Reinert, 1970
Lake herring, Coregonus artedi	2,236,666	field	Reinert, 1970
Lake whitefish, Coregonus clupeaformis	260,000	field	Reinert, 1970
Bloater, Coregonus hoyi	2,870,000	field	Reinert, 1970
Kiyi, Coregonus kiyi	4,426,666	field	Reinert, 1970
Cisco, Coregonus sp.	368,777	field	Miles & Harris, 1973
Coho salmon, Oncorhynchus kisutch	1,563,571	field	Lake Michigan Interstate Pestic. Comm. 1972
Rainbow trout, Salmo gairdneri	181,000	108	Hamelink & Waybrant, 1976
Rainbow trout, Salmo gairdneri	11,607	field	Miles & Harris, 1973

Table 5. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Rainbow trout, Salmo gairdneri	38,642	84	Reinert, et al. 1974
Brown trout, Salmo trutta	45,357	field	Miles & Harris, 1973
Lake trout, Salvelinus namaycush	458,259	field	Miles & Harris, 1973
Lake trout, Salvelinus namaycush	1,168,333	field	Reinert, 1970
Lake trout, Salvelinus namaycush	47,428	152	Reinert & Stone, 1974
American smelt, Osmerus mordax	770,000	field	Reinert, 1970
Carp, Cyprinus carpio	640,000	field	Reinert, 1970
Common shiner (composite), Notropis cornutus Northern redbelly dace, Chrosomus eos	363,000	40	Hamelink, et al. 1971
Fathead minnow, Pimephales promelas	99,000	266	Jarvinen, et al. 1977
White sucker, Catostomus commersoni	110,000	field	Miles & Harris, 1973
White sucker, Catostomus commersoni	96,666	field	Reinert, 1970
Trout-perch, Percopsis omiscomaycus	313,333	field	Reinert, 1970
Flagfish, Jordanella floridiae	14,526	field	Kolipinski, et al. 1971
Mosquitofish, Gambusia affinis	21,411	field	Kolipinski, et al. 1971
Rock bass, Ambloplites rupestris	17,500	field	Miles & Harris, 1973
Green sunfish, Lepomis cyanellus	17,500	15	Sanborn, et al.. 1975

Table 5. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Green sunfish (composite), Lepomis cyanellus Pumpkinseed, Lepomis gibbosus	59,210	80	Hamelink, et al. 1971
Bluegill, Lepomis macrochirus	110,000	60	Hamelink & Waybrant, 1976
Bluegill, Lepomis macrochirus	16,071	field	Miles & Harris, 1973
Largemouth bass (young of year), Micropterus salmoides	317,000	40	Hamelink, et al. 1971
Yellow perch, Perca flavescens	1,073,333	field	Reinert, 1970
Slimy sculpin, Cottus cognatus	763,333	field	Reinert, 1970

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Man	Edible fish and shellfish	5	U.S. FDA Admin. Guideline 7420.08, 1973
Domestic animals	Animal feed	0.5	U.S. FDA Admin. Guideline 7426.04, 1977
Mallard, Anas platyrhynchos	Eggshell thinning	3*	Haseltine, et al. 1974
Mallard, Anas platyrhynchos	Eggshell thinning	3*	Heath, et al. 1969
Black duck, Anas rubripes	Eggshell thinning	3*	Longcore, et al. 1971
Black duck, Anas rubripes	Reduced duckling survival	2.8	Longcore & Stendell. 1977
Sparrow hawk, Falco sparverius	Eggshell thinning	3	Lincer, 1975
Sparrow hawk, Falco sparverius	Reduced survival	2.8	Porter & Wiemeyer, 1972

Table 5. (Continued)

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Screech owl, *Otus asio*	Eggshell thinning	2.8	McLane & Hall, 1972
Brown pelican, *Pelecanus occidentalis*	Eggshell thinning	0.5	Blus, et al. 1972,1974
Brown pelican, *Pelecanus occidentalis*	Reduced productivity	0.15	Anderson, et al. 1975
Coho salmon (fingerling), *Onchorhynchus kisutch*	Reduced survival	6.25	Buhler, et al. 1969
Chinook salmon (fingerling), *Onchorhynchus tshawytscha*	Reduced survival	6.25	Buhler, et al. 1969
Cutthroat trout, *Salmo clarki*	Reduced sac fry survival	3	Allison, et al. 1963
Rainbow trout, *Salmo gairdneri*	Inhibition of Na^+-K^+ ATPase	2.75	Campbell, et al. 1974
Rainbow trout, *Salmo gairdneri*	Reduced phenoxyethanol anesthetic induction and recovery times	11.36	Klaverkamp, et al. 1976
Rainbow trout, *Salmo gairdneri*	Reduced light intensity discrimination	9	McNicholl & Mackay, 1975
Brown trout, *Salmo trutta*	Reduced fry survival	3.4	Burdick, et al. 1972
Lake trout, *Salvelinus namaycush*	Reduced fry survival	6	Burdick, et al. 1972

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* Value converted from dry weight to wet weight basis

Average fish bioconcentration factor = 640,000

Lowest permissible tissue concentration = 0.15 mg/kg

$$\frac{0.15}{640{,}000} = .00000023 \text{ mg/kg or } .00023\ \mu\text{g/l}$$

Table 6. Other freshwater data for DDT and metabolites

Organism	Test Duration	Effect	Result (ug/l)	Reference
Cladoceran, Daphnia magna	14 days	LC50	0.67	Maki & Johnson, 1975
Cladoceran, Daphnia magna	14 days	50% inhibition of total young produced	0.50	Maki & Johnson, 1975
Scud, Gammarus fasciatus	120 hrs	LC50	0.6	Sanders, 1972
Glass shrimp, Palaemonetes kadiakensis	36 hrs	LC50	4.5	Ferguson, et al. 1965b
Glass shrimp, Palaemonetes kadiakensis	120 hrs	LC50	1.3	Sanders, 1972
Stonefly (naiad), Acroneuria pacifica	30 days	LC50	72	Jensen & Gaufin, 1964
Stonefly (naiad), Pteronarcys california	30 days	LC50	265	Jensen & Gaufin, 1964
Planarian, Polycelis felina	24 days	Asexual fission inhibition	250	Kouyoumjian & Uglow, 1974
Coho salmon, Oncorhynchus kisutch	-	Reduced fry survival	1.09 mg/kg in eggs	Johnson & Pecor, 1969
Coho salmon (juvenile), Oncorhynchus kisutch	7 days	Increased cough frequency	5	Schaumburg, 1967
Coho salmon, Oncorhynchus kisutch	125 days	Estimated median survival time-106 days	1.27 mg/kg in food	Buhler & Shanks, 1972
Cutthroat trout, Salmo clarki	-	Reduced sac fry survival	>0.4 mg/kg in eggs	Cuerrier, et al. 1967
Rainbow trout, Salmo gairdneri	24 hrs	Uncontrolled reflex reaction	100	Peters & Weber, 1977
Rainbow trout, Salmo gairdneri	5 hrs	Cough response threshold	52-140	Lunn, et al. 1976

Table 6. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Rainbow trout, Salmo gairdneri	-	Reduced sac fry survival	>0.4 mg/kg in eggs	Cuerrier, et al. 1967
Atlantic salmon (gastrulae), Salmo salar	30 days	Retarded behavioral development and impaired balance of alevins	50	Dill & Saunders, 1974
Atlantic salmon, Salmo salar	24 hrs	Altered temperature selection	5	Ogilvie & Anderson, 1965
Atlantic salmon Salmo salar	24 hrs	Altered temperature selection for 1 mo	50	Ogilvie & Miller, 1976
Atlantic salmon, Salmo salar	24 hrs	Altered temperature selection	10	Peterson, 1973
Brook trout, Salvelinus fontinalis	24 hrs	Lateral line nerve hypersensitivity	100	Anderson, 1968
Brook trout, Salvelinus fontinalis	24 hrs	Visual conditioned avoidance inhibition	20	Anderson & Peterson, 1969
Brook trout, Salvelinus fontinalis	-	Reduced sac fry survival	>0.4 mg/kg in eggs	Cuerrier, et al. 1967
Brook trout, Salvelinus fontinalis	24 hrs	Altered temperature selection	20	Gardner, 1973
Brook trout, Salvelinus fontinalis	156 days	Slight reduction in sac fry survival	2 mg/kg in food	Macek, 1968
Brook trout, Salvelinus fontinalis	24 hrs	Altered temperature selection	10	Miller & Ogilvie, 1975
Brook trout, Salvelinus fontinalis	24 hrs	Altered temperature selection	100	Peterson, 1973
Lake trout (fry), Salvelinus namaycush	-	Reduced survival	2.9 mg/kg in fry	Burdick, et al. 1964
Goldfish, Carassius auratus	2.5 hrs	Loss of balance and decreased spontaneous electrical activity of the cerebellum	1,000	Aubin & Johansen, 1969

Table 6. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Goldfish, *Carassius auratus*	4 days	Exploratory behavior inhibition	10	Davy & Kleerekoper, 1973
Goldfish, *Carassius auratus*	7 days	Schooling inhibition	1	Weis & Weis, 1974
Golden shiner, *Notemigonus crysoleucas*	24 hrs	Schooling inhibition	15	Baily, 1973
Golden shiner, *Notemigonus crysoleucas*	36 hrs	LC50	29.9	Ferguson, et al. 1964
Fathead minnow, *Pimephales promelas*	266 days	Mg^{2+} ATPase inhibition	0.5	Desaiah, et al. 1975
Black bullhead, *Ictalurus melas*	36 hrs	LC50	16.4	Ferguson, et al. 1965a
Mosquitofish, *Gambusia affinis*	36 hrs	LC50	21.3	Ferguson, et al. 1965a
Mosquitofish, *Gambusia affinis*	40 min	Succinic dehydrogenase activity inhibition	9×10^{-9} molar	Moffett & Yarbrough, 1972
Green sunfish, *Lepomis cyanellus*	36 hrs	LC50	23.5	Ferguson, et al. 1964
Bluegill, *Lepomis macrochirus*	36 hrs	LC50	28.7	Ferguson, et al. 1964
Bluegill, *Lepomis macrochirus*	16 days	Hyperactive locomotor response	0.008	Ellgaard, et al. 1977
Toad (tadpole, 4-5-wk-old), *Bufo woodhousei fowleri*	96 hrs	LC50	1,000	Sanders, 1970
Toad (tadpole, 4-5-wk-old), *Bufo woodhousei fowleri*	96 hrs	LC50 (TDE)	140	Sanders, 1970
Toad (tadpole, 6-wk-old), *Bufo woodhousei fowleri*	96 hrs	LC50	100	Sanders, 1970

Table 6. (Continued)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Toad (tadpole, 7-wk-old), *Bufo woodhousei fowleri*	96 hrs	LC50	30	Sanders, 1970
Frog (tadpole), *Pseudacris triseriata*	96 hrs	LC50	800	Sanders, 1970
Frog (tadpole), *Pseudacris triseriata*	96 hrs	LC50 (TDE)	400	Sanders, 1970
Frog (tadpole), *Rana clamitans*	6 days	Increased pituitary melanocyte-stimulating hormone levels	100	Peaslee, 1970
Turtle, *Chrysemys picta*	30 min	ATPase inhibition	0.53 µM	Phillips & Wells, 1974

Lowest value = 0.008 µg/l

SALTWATER ORGANISMS

Introduction

DDT, a chlorinated hydrocarbon insecticide, was at one time the most widely used compound for the control of insect pests. It was applied for more than 30 years to a variety of environments, including the aquatic environment, in many forms (such as powders, emulsions, encapsulations).

Despite the widespread use of DDT, relatively few data are available that describe its chronic effects on aquatic animals. No saltwater life-cycle toxicity test has been conducted and only one such study using a freshwater animal has been published.

Any examination of environmental contamination by a pesticide must include a consideration of its persistence which may be beneficial or harmful. Long-lived pesticides provide control of target organisms over longer periods of time and reduce the need for reapplication, but may also affect non-target flora and fauna for long periods of time. DDT is recognized as a persistent pesticide.

Because of its persistent nature, coupled with hydrophobic properties and solubility in lipids, DDT and its metabolites are concentrated by aquatic organisms from water, enter the food web and are bioaccumulated by organisms at higher trophic levels.

DDT has several metabolites. In environmental samples, the two most frequent metabolites reported are DDD (TDE or Rhothane) and DDE. Rhothane was manufactured as an insecticide and used for a number of years. Most of the available aquatic toxicity data are for DDT. However, because of their widespread occurrence, DDD and DDE must be considered, particularly for their toxicities to consumer species and occurrence in monitoring programs.

Thus, a derivation of a DDT criterion must consider not only acute and chronic toxicity to aquatic organisms, but also 1) its persistence, 2) its propensity for bioaccumulation, 3) its breakdown into longlived metabolites, and 4) the toxicity of DDT and its metabolites to organisms at higher trophic levels, such as birds of prey, as a result of food chain bioaccumulation.

Acute Toxicity, DDT

In flow-through exposures with unmeasured concentrations, the unadjusted LC50 values (Table 7) for nine fish species ranged from 0.20 to 3.4 µg/l (Schoettger, 1970; Lowe, unpublished data; Korn and Earnest, 1974; Earnest and Benville, 1971).

Static tests results were also reported for nine species with the adjusted LC50 values ranging from 0.2 to 4.2 µg/l (Eisler, 1970a,b; Earnest and Benville, 1971). Two species were tested in static and flow-through tests under similar temperature and salinity conditions (Earnest and Benville, 1971) and a comparison of the results indicates that LC50 values from static tests are approximately 15 times higher than those in flowthrough tests. Therefore, the 0.71 adjustment factor for this test condition may be too high for DDT.

Adjusted LC50 values (Table 8) for flow-through tests with DDT and invertebrate species ranged from 0.14 to 3.3 µg/l (Lowe, unpublished data; Schimmel and Patrick, 1975; Schoettger, 1970). The adjusted 96-hour LC50 values for three invertebrate species obtained from static tests ranged from 0.5 to 3.0 µg/l (Eisler, 1969; Schoettger, 1970). The most sensitive saltwater invertebrat species tested were the commercially important white shrimp with an LC50 value of 0.1 μg/l (Lowe, unpublished data) and the Korean shrimp with an LC50 of 0.13 μg/l (Schoettger, 1970). The Korean shrimp was exposed to DDT in both flow-through and static tests under similar temperature and salinity conditions (Schoettger, 1970). The results indicated that the result of the static LC50 was more than five times greater than that in the flow-through test. Thus, the invertebrate adjustment factor of 1.1 times the static LC50 may be inappropriate.

Acute Toxicity, DDD and DDE

The acute toxicity of the DDT metabolite, DDD, to three species of fish is reported in Table 7. In flow-through exposures using unmeasured concentrations, the adjusted 96-hour LC50 values for the three species ranged from 1.9 to 26.2 μg/l (Lowe, unpublished data; Korn and Earnest, 1974). Of the three species, Morone saxatilis (Korn and Earnest, 1974), and Fundulus similis (Lowe, unpublished data) were exposed to both DDD and DDE under similar temperature and salinity conditions. A comparison of the results indicates that DDD was one-fifth to one-seventh as acutely toxic to these species as was DDT.

Acute toxicity results for saltwater invertebrate species exposed to DDD and DDE are reported in Table 8. Flow-through adusted 48- or 96-hour EC50 or LC50 values for three invertebrate species ranged from 1.2 to 19.3 μg DDD/l (Lowe, unpublished data; Schoettger, 1970). The 96-hour LC50 in static exposures of Korean shrimp to DDD was 8.3 μg/l and in flow-through exposures was 1.6 μg/l (Schoettger, 1970). Flow-through adjusted LC50 values for the Eastern oyster and the brown shrimp exposed to DDE were 10.8

(96-hour) to 9.3 (48-hour) µg/l, respectively (Lowe, unpublished data). Of the invertebrate species tested, the most sensitive to DDT, DDD and DDE, appear to be the pink shrimp and the Korean shrimp.

Chronic Toxicity

Concentrations of DDT affecting three saltwater invertebrate species in long-term exposures did not differ greatly from 48- or 96-hour LC50 values. Concentrations of DDT affecting shell deposition of the eastern oyster in seven days (10 µg/l; Butler, 1966) and DDT concentrations resulting in mortality of the blue crab in 36 weeks (0.5 µg/l; Lowe, 1965) and pink shrimp in 28 days (0.12 µg/l; Nimmo, et al. 1970) were similar to LC50 values in acute exposures of two to four days duration (Table 8 and 11). These data cannot be used to calculate an Invertebrate Chronic Value because none of the above species were exposed during the reproductive portions of their life-cycle.

Plant Effects

Information on the sensitivity of aquatic plants including algae and rooted vascular plants, while limited, indicates that they are much less sensitive to DDT than are fish or invertebrate species (Table 9). DDT at concentrations of 10 µg/l has been found to reduce photosynthesis in saltwater diatoms, green algae, and dinoflagellates (Wurster, 1968).

Residues

Several laboratory tests have investigated the bioconcentration of DDT in tissues of saltwater animals (Table 10). Bioconcentration factors (BCF) in these studies ranged from 1,200 to 76,300 for fish or shellfish (Butler, 1966; Lowe et al., 1978;

Nimmo, et al. 1970; and Hansen and Wilson, 1970). Eastern oysters exhibited BCF values from 10,000 for a 12-day exposure (Butler, 1966) to 76,300 for a 168-day exposure (Lowe, et al. 1971); the former study was probably not of sufficient duration for DDT to accumulate to steady-state. Parrish (1974) exposed oysters to DDT and metabolites for 392 days and reported a bioconcentration factor of 37,000 times the nominal exposure concentration (Table 11); he noted that concentrations in tissues were a function of spawning activity (i.e., concentrations were highest immediately prior to spawning and lowest after spawning).

Bioconcentration factors for DDT determined from saltwater animals captured from their natural environments were comparable with those from laboratory studies (Table 10). BCF's in these studies ranged from 800 times for unspecified zooplankton (Woodwell, et al. 1967) to 46,500 times for the dwarf perch, Micrometrus minimus (Earnest and Benville, 1971).

Several studies have addressed the problem of concentrations of DDT and metabolites in food and saltwater organisms and avian predator species. Odum, et al. (1969) fed fiddler crabs a diet of natural detritus containing DDT residues of 10 mg/kg. After five days, crabs fed DDT-contaminated detritus exhibited extremely poor coordination. Although no crabs died, such behavior would "almost certainly affect survival under natural conditions." After eleven days on the diet, the DDT and metabolites increased threefold in their tissues to 0.885 mg/kg. Odum, et al. (1969) speculated that the results of this study may help to explain the disappearance of this species from a Long Island marsh sprayed with DDT for more than 15 years.

Avian species that feed on saltwater animals containing DDT and metabolites (particularly DDE) have exhibited reductions in their reproductive capacity. For example, a colony of Bermuda petrels, a species which feeds primarily on cephalopods in the North Atlantic, suffered a significant decline in their population from 1958 to 1967 (Wurster, 1968). Analysis of unhatched eggs and dead chicks revealed an average concentration of 6.4 mg/kg DDT and metabolites (62 percent DDE). No data are available on the concentrations of DDT and metabolites in the cephalopods consumed by the petrels.

Two studies evaluated the effects of DDT and metabolites in eggs of the brown pelican and the subsequent decrease in reproductive success. Blus, et al. (1974) reported that their reproductive success was normal only when concentrations of DDT (including metabolites) and the insecticide, dieldrin, were less than 2.5 mg/kg and 0.54 mg/kg, respectively. Anderson, et al. (1975) studied the breeding success of the brown pelican in relation to residues of DDT and metabolites in their eggs and in their major food source, the northern anchovy. Their analyses of data collected from 1969 to 1974 included the following observations: (1) residues of DDT and metabolites (the major compound was DDE) in northern anchovies dropped steadily from a mean of 4.3 mg/kg (wet weight) in 1969 to 0.15 mg/kg in 1974; (2) during that same period, DDT and metabolites in intact eggs averaged 907 mg/kg (lipid weight) in 1969 to 97 mg/kg in 1974, and higher residues were associated with crushed eggs; and (3) productivity of pelicans increased from a total of four young fledged in 1969 to 1,115 fledged in 1974, with a concurrent increase in eggshell thickness.

Anderson, et al. (1975) stated that even the lowest concentration of DDT and metabolites in northern anchovies (0.15 mg/kg) and the subsequent 97 mg/kg concentration in pelican eggs were unacceptably high, because the pelican eggshell thickness was below normal and productivity was too low for population stability.

If data of Anderson, et al. (1975) are used to calculate a Residue Limited Toxicant Concentration (RLTC), the maximum concentrations of DDT and metabolites allowable in fish would be less than 0.15 mg/kg. The average fish BCF from Table 10 is 22,467. The RLTC is, therefore, less than 0.0067 µg/l. Because the maximum concentration in fish is a concentration affecting pelicans, a criterion based on this RLTC must be lower.

It is noteworthy that none of the fishes tested in Table 10 is a species that belong to the order Clupeiformes. Cluepeids are a major food source for brown pelicans and are very high in lipid content. Due to the lipophilic nature of DDT and its metabolites, it is likely that these fishes would contain higher concentrations of the insecticide than would fishes of lower lipid content such as those listed in Table 10. Therefore, the average bioconcentration factor for fishes (22,467) listed in Table 10 may underestimate the concentration factors likely to occur in cluepeid species. Because no no-effect concentration in food of pelicans is known and because the bioconcentration factor for fish is probably too low, and RLTC based on these data is not likely to be protective.

Miscellaneous

No other data from Table 11 suggest any more sensitive effects.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 0.38 μg/l

Final Invertebrate Acute Value = 0.021 μg/l

Final Acute Value = 0.021 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 10 μg/l

Residue Limited Toxicant Concentration = 0.0067 μg/l

Final Chronic Value = 0.0067 μg/l

0.44 x Final Acute Value = 0.0092 μg/l

No saltwater criterion can be derived for DDT and metabolites using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

Results obtained with DDT and metabolites and freshwater organisms indicate how a criterion may be estimated for DDT and metabolites and saltwater organisms.

For DDT and metabolites and freshwater organisms the Residue Limited Toxicant Concentration is lower than the Final Fish Chronic Value which is derived from results of a life cycle test with the fathead minnow. Therefore, it seems reasonable to estimate a criterion for DDT and metabolites and saltwater organisms using the Residue Limited Toxicant Concentration as the Final Chronic Value.

The maximum concentration of DDT and metabolites is the Final Acute Value of 0.021 µg/l and the estimated 24-hour average concentration is the Final Chronic Value of 0.0067 µg/l. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For DDT and metabolites the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 0.0067 µg/l as a 24-hour average and the concentration should not exceed 0.021 µg/l at any time.

Table 7. Marine fish acute values for DDT and metabolites

Organism	Bioassay Method *	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American eel, Anguilla rostrata	S	U	96	4	2.2	Eisler, 1970b
Chinook salmon Oncorhynchus tshawytscha	FT	U	96	0.68	0.52	Schoettger, 1970
Sheepshead minnow, Cyprinodon variegatus	FT	U	48	3.2	2	Lowe, undated
Sheepshead minnow, Cyprinodon variegatus	FT	U	48	2	1.2	Lowe, undated
Mummichog, Fundulus heteroclitus	S	U	96	3	1.6	Eisler, 1970a
Mummichog, Fundulus heteroclitus	S	U	96	5	2.7	Eisler, 1970b
Striped killifish, Fundulus majalis	S	U	96	1	0.55	Eisler, 1970b
Longnose killifish, Fundulus similis	FT	U	48	42***	26.2	Lowe, undated
Longnose killifish, Fundulus similis	FT	U	48	5.5	3.4	Lowe, undated
Atlantic silverside, Menidia menidia	S	U	96	0.4	0.2	Eisler, 1970b
Striped bass, Morone saxatilis	FT	U	96	0.53	0.41	Korn & Earnest, 1974
Striped bass, Morone saxatilis	FT	U	96	2.5***	1.9	Korn & Earnest, 1974
Pinfish, Lagodon rhomboides	FT	U	48	0.32	0.20	Lowe, undated
Spot, Leiostomus xanthurus	FT	U	48	1.8	1.1	Lowe, undated
Spot, Leiostomus xanthurus	FT	U	48	20***	12.5	Lowe, undated

Table 7. (Continued)

Organism	Bioassay Method *	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Shiner perch, *Cymatogaster aggregata*	S	U	96	7.6	4.2	Earnest & Benville, 1971
Shiner perch, *Cymatogaster aggregata*	FT	U	96	0.45	0.35	Earnest & Benville, 1971
Dwarf perch, *Micrometrus minimus*	S	U	96	4.6	2.5	Earnest & Benville, 1971
Dwarf perch, *Micrometrus minimus*	FT	U	96	0.26	0.20	Earnest & Benville, 1971
Bluehead, *Thalassoma bifasciatum*	S	U	96	7	3.8	Eisler, 1970b
Mullet, *Mugil cephalus*	S	U	96	0.9	0.5	Eisler, 1970b
Mullet, *Mugil cephalus*	S	U	96	3	1.6	Eisler, 1970b
Mullet, *Mugil cephalus*	FT	U	48	0.4	0.2	Lowe, undated
Mullet, *Mugil cephalus*	FT	U	48	0.55	0.3	Lowe, undated
Mullet, *Mugil cephalus*	FT	U	48	0.4	0.2	Lowe, undated
Northern puffer, *Sphaeroides maculatus*	S	U	96	89	48.6	Eisler, 1970b

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* S = static; FT = flow-through

** M = measured; U = unmeasured

***DDD

Geometric mean of adjusted values = 1.37 μg/l $\frac{1.37}{3.7}$ = 0.38 μg/l

Table 8. Marine invertebrate acute values for DDT and metabolites

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Eastern oyster, Crassostrea virginica	FT	U	96	7	5.4	Lowe, undated
Eastern oyster, Crassostrea virginica	FT	U	96	9	6.9	Lowe, undated
Eastern oyster, Crassostrea virginica	FT	U	96	14****	10.8	Lowe, undated
Eastern oyster, Crassostrea virginica	FT	U	96	25***	19.3	Lowe, undated
Brown shrimp, Penaeus aztecus	FT	U	48	28****	9.3	Lowe, undated
Brown shrimp, Penaeus aztecus	FT	U	48	1	0.3	Lowe, undated
Brown shrimp, Penaeus aztecus	FT	M	96	0.14	0.14	Schimmel & Patrick, 1975
Pink shrimp, Penaeus duorarum	FT	U	48	2.4***	0.79	Lowe, undated
Pink shrimp, Penaeus duorarum	FT	U	48	0.6	0.2	Lowe, undated
White shrimp, Penaeus setiferus	FT	U	24	0.7	0.1	Lowe, undated
Grass shrimp, Palaemonetes pugio	FT	U	48	0.8	0.3	Lowe, undated
Grass shrimp, Palaemonetes vulgaris	S	U	96	2	1.7	Eisler, 1969
Sand shrimp, Crangon septemspinosa	S	U	96	0.6	0.5	Eisler, 1969
Korean shrimp, Palaemon macrodactylus	S	U	96	0.86	0.73	Schoettger, 1970
Korean shrimp, Palaemon macrodactylus	FT	U	96	0.17	0.13	Schoettger, 1970

Table 8. (Continued)

Organism	Bioassay Method *	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Korean shrimp, *Palaemon macrodactylus*	S	U	96	8.3***	7	Schoettger, 1970
Korean shrimp, *Palaemon macrodactylus*	FT	U	96	1.6***	1.2	Schoettger, 1970
Blue crab, *Callinectes sapidus*	FT	U	48	10	3.3	Lowe, undated
Hermit crab, *Pagurus longicarpus*	S	U	96	6	5.1	Eisler, 1969

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* S = static; FT = flow-through

** M = measured; U = unmeasured

*** DDD

****DDE

Geometric mean of adjusted value = 1.01 µg/l $\frac{1.01}{49} = 0.021$

Lowest value from flow-through test based on measured concentrations = 0.14 µg/l

Table 9. Marine plant effects for DDT and metabolites (Wurster, 1968)

Organism	Effect	Concentration (µg/l)
Diatom, *Skeletonema costatum*	Reduced photosynthesis	10
Coccolithophore, *Coccolithus huxlegi*	Reduced photosynthesis	10
Green alga, *Pyramimonas sp*.	Reduced photosynthesis	10
Neritic dinoflagellate, *Peridinium trochoideum*	Reduced photosynthesis	10

Lowest plant value = 10 µg/l

Table 10. Marine residues for DDT and metabolites

Organism	Bioconcentration Factor	Time (days)	Reference
Zooplankton, species not given	800*	field	Woodwell, et al. 1967
Mud snail, Nassarius obsoletus	5,200*	field	Woodwell, et al. 1967
Hard clam, Mercenaria mercenaria	8,400*	field	Woodwell, et al. 1967
Eastern oyster, Crassostrea virginica			
males	20,000**	12	Butler, 1966
females	14,000**	12	Butler, 1966
males and females	10,000**	12	Butler, 1966
Gametes			
eggs	25,000**	12	Butler, 1966
sperm	9,000**	12	Butler, 1966
Eastern oyster, Crassostrea virginica	42,200**	252	Lowe, et al. 1970
Eastern oyster, Crassostrea virginica	76,300**	168	Lowe, et al. 1970
Pink shrimp, Penaeus duorarum	1,500**	13	Nimmo, et al. 1970
Pink shrimp, Penaeus duorarum	1,200**	56	Nimmo, et al. 1970
Shrimp, species not given	3,200*	field	Woodwell, et al.. 1967
Market crab, Cancer magister	14,250*	field	Earnest & Benville, 1971
Market crab, Cancer magister	4,750*	field	Earnest & Benville, 1971
American eel, Anguilla rostrata	5,600*	field	Woodwell, et al. 1967

Table 10. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Oyster toadfish, Opsanus tau	3,400*	field	Woodwell, et al. 1967
Atlantic needlefish, Strongylura marina	41,400*	field	Woodwell, et al. 1967
Sheepshead minnow, Cyprinodon variegatus	18,800*	field	Woodwell, et al. 1967
Mummichog, Fundulus heteroclitus	24,800*	field	Woodwell, et al. 1967
Atlantic silverside, Menida menida	4,600*	field	Woodwell, et al. 1967
Threespine stickleback, Gasterosteus aculeatus	5,200*	field	Woodwell, et al. 1967
Pinfish, Lagodon rhomboides	40,000**	14	Hansen, 1970
Pinfish, Lagodon rhomboides	11,000**	14	Hansen, 1970
Atlantic croaker, Micropogon undulatus	16,000**	21-35	Hansen, 1970
Atlantic croaker, Micropogon undulatus	12,200**	14	Hansen, 1970
Shiner perch, Cymatogaster aggregata	43,250*	field	Earnest & Benville, 1971
Shiner perch, Cymatogaster aggregata	34,750*	field	Earnest & Benville, 1971
Dwarf perch, Micrometrus minimus	46,500*	field	Earnest & Benville, 1971
Dwarf perch, Micrometrus minimus	37,000*	field	Earnest & Benville, 1971
White perch, Phanerodon fureatus	22,250*	field	Earnest & Benville, 1971
White perch, Phanerodon fureatus	29,250*	field	Earnest & Benville, 1971

Table 10. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Pile perch, Racochilus vacca	26,750*	field	Earnest & Benville, 1971
Pile perch, Raccochilus vacca	32,500*	field	Earnest & Benville, 1971
Staghorn sculpin, Leptocotlus armatus	17,000*	field	Earnest & Benville, 1971
Staghorn sculpin, Leptocotlus armatus	22,250*	field	Earnest & Benville, 1971
Summer flounder, Paralichthys dentatus	25,600*	field	Woodwell, et al. 1967
Speckled sanddab, Citharichthys stigmaeus	15,250*	field	Earnest & Benville, 1971
Speckled sanddab, Citharichthys stigmaeus	12,250*	field	Earnest & Benville, 1971
English sole, Parophrys vetulus	20,000*	field	Earnest & Benville, 1971
English sole, Parophrys vetulus	13,000*	field	Earnest & Benville, 1971
Starry flounder, Platichthys stellatus	24,750*	field	Earnest & Benville, 1971
Starry flounder, Platichthys stellatus	23,750*	field	Earnest & Benville, 1971

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Man	Edible fish and shellfish	5	U.S. FDA Admin. Guideline 7420.08, 1973
Domestic animals	Animal feed	0.5	U.S. FDA Admin. Guideline 7426.04, 1977
Mallard, Anas platyrhynchos	Eggshell thinning	3***	Haseltine, et al. 1974

Table 10. (Continued)

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Mallard, Anas platyrhynchos	Eggshell thinning	3***	Heath, et al. 1969
Black duck, Anas rubripes	Eggshell thinning	3***	Longcore, et al. 1971
Black duck, Anas rubripes	Reduced duckling survival	2.8	Longcore & Stendell, 1977
Sparrow hawk, Falco sparverius	Eggshell thinning	3	Lincer, 1975
Sparrow hawk, Falco sparverius	Reduced survival	2.8	Porter & Wiemeyer, 1972
Screech owl, Otus asio	Eggshell thinning	2.8	McLane & Hall, 1972
Brown pelican, Pelecanus occidentalis	Eggshell thinning	0.5	Blus, et al. 1972, 1974
Brown pelican, Pelecanus occidentalis	Reduced productivity	0.15	Anderson, et al. 1975
Coho salmon (fingerling), Oncorhynchus kisutch	Reduced survival	6.25	Buhler, et al. 1969
Chinnok salmon (fingerling), Oncorhynchus tshawytscha	Reduced survival	6.25	Buhler, et al. 1969
Cutthroat trout, Salmo clarki	Reduced sac fry survival	3	Allison, et al. 1963
Rainbow trout, Salmo gairdneri	Inhibition of Na^+-K^+ ATPase	2.75	Campbell, et al. 1974
Rainbow trout, Salmo gairdneri	Reduced phenoxyethanol anesthetic induction and recovery times	11.36	Klaverkamp, et al. 1976
Rainbow trout, Salmo gairdneri	Reduced light intensity discrimination	9	McNicholl & Mackay, 1975
Brown trout Salmo trutta	Reduced fry survival	3.4	Burdick, et al. 1972

Table 10. (Continued)

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Lake trout, Salvelinus namaycush	Reduced fry survival	6	Burdick, et al. 1972

* Field data (including metabolites when given)

** Laboratory data (including metabolites when given)

*** Value converted from dry weight to wet weight basis

Average bioconcentration for fishes = 22,467

Average bioconcentration factor for pelecypods = 28,000

Lowest permissible tissue concentration = 0.15 mg/kg

$\frac{0.15}{22,467}$ = 0.0000067 mg/kg or 0.0067 μg/l

Table 11. Other marine data for DDT and metabolites

Organism	Test Duration	Effect	Result (ug/l)	Reference
Eastern oyster, Crassostrea virginica	7 days	Affected shell deposition	10	Butler, 1966
Eastern oyster, Crassostrea virginica	392 days	Bioconcentration factor = 37,000*	-	Parrish, 1974
Pink shrimp, Penaeus duorarum	30 days	Affected cation concentrations in hepatopancreas tissue.	0.05	Nimmo & Blackman, 1972
Blue crabs, Callinectes sapidus	36 wks	Mortality	0.50	Lowe, 1965
Mummichog, Fundulus heteroclitus	240 hrs	LC50	2.7	Eisler, 1970
Mosquitofish, Gambusia affinis	24 hrs	Affected salinity selection	5-20	Hansen, 1972
Pink shrimp, Penaeus duorarum	28 days	LC100	0.12	Nimmo, et al. 1970

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* Result based on unmeasured water concentrations.

DDT

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

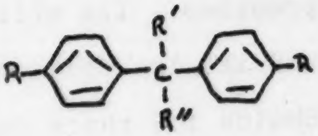
DDT, first synthesized in Germany in 1874, has been used extensively world-wide for public health and agricultural programs. Its efficacy as a broad spectrum insecticide and its low cost continue to make it the insecticide of choice for those measures for most of the world.

Following an extensive review of health and environmental hazards of the use of DDT, U.S. EPA decided to ban further use of DDT. This decision was based on several properties of DDT that had been well evidenced: (1) DDT and its metabolites are toxicants with long-term persistence in soil and water, (2) it is widely dispersed by erosion, runoff and volatilization, (3) the low-water solubility and high lipophilicity of DDT result in concentrated accumulation of DDT in the fat of wildlife and humans which may be hazardous. Agricultural use of DDT was canceled by the U.S. EPA in December, 1972. Prior to this, DDT had been widely used in the U.S. with a peak usage in 1959 of 80 million pounds. This amount decreased steadily to less than 12 million pounds by 1972. Since the 1972 ban, the use of DDT in the U.S. has been effectively discontinued.

The purpose of this report is to briefly summarize the published reviews in literature with special attention to the mutagenic and carcinogenic effects of DDT and its metabolites. Within the text, the following abbreviations and their meanings are hereby noted.

DDT refers to technical DDT, which is usually composed of:

- 77.1% p,p'-DDT
- 14.9% o,p'-DDT
- 0.3% p,p'-DDD
- 0.1% o,p'-DDD
- 4.0% p,p'-DDE
- 0.1% o,p'-DDE
- 3.5% unidentified compounds



		R	R'	R"
DDT	1,1'-(2,2,2-trichloroethylidene)-bis/4-chlorobenzene/	-Cl	-H	$-CCl_3$
DDE	1,1'-(2,2-dichloroethenylidene)-bis/4-chlorobenzene/	-Cl	None	$=CCl_2$
DDD	1,1'-(2,2-dichloroethylidene)-bis/4-chlorobenzene/	-Cl	-H	$-CHCl_2$
DDMU	1,1'-(2-chloroethenylidene)-bis/4-chlorobenzene/	-Cl	None	-CHCl
DDMS	1,1'-(2-chloroethylidene)-bis/4-chlorobenzene/	-Cl	-H	$-CH_2Cl$
DDNU	1,1-bis(4-chlorophenyl) ethylene	-Cl	None	$=CH_2$
DDOH	2,2-bis(4-chlorophenyl) ethanol	-Cl	-H	$-CH_2OH$
DDA	2,2-bis(4-chlorophenyl)-acetic acid	-Cl	-H	-C(O)OH

Ingestion from Water

The solubility of DDT in water is approximately 1.2 ppb, although the presence of salts, colloid and particulate material may increase this solubility. An examination of Table 1 shows no instance of natural water approaching the solubility limit (Bevenue, 1976). Lichtenberg, et al. (1970) noted that residues in surface water peaked in 1966 and tapered down in 1967 and 1968, and this trend should be continuing. Since the primary source of DDT residues in surface waters is runoff from drainage areas, the variations seen in samplings range from non-detectable to 1 ppb and are the result of variable seasonal runoff patterns, sedimentation rates, amount of pesticides on land areas, and distance of travel from points of application.

By utilizing the guidelines for deriving water quality criterion for the protection of aquatic life (43FR29028, July 1978), maximum concentrations of DDT in fresh water were calculated. To protect freshwater aquatic organisms and consumers of these organisms, a twenty-four hour average concentration of DDT of 0.00023 ug/l and a maximum concentration of 0.41 ug/l were proposed as standards. The chronic levels proposed are near the limits of detection and subject to significant analytical error (Gunther, 1969). The low chronic level proposed may be a reflection of the large bioaccumulation factor used in this model.

The National Academy of Sciences Safe Drinking Water Committee estimates the carcinogenic risk to man to be an excess death rate of 63 persons per year at a 10 ug/l expo-

TABLE 1

DDT and Metabolites in Waters of Different Areas (Bevenue, 1976)

Water Sources	Time Period	ppt Range	Reference
Galveston Bay (Gulf of Mexico)	1964	N.D.-1,000	Casper (1967)
Selected Western Streams (USA)	1965-1966	N.D.-120	Brown and Nishioka (1967)
Selected Western Streams (USA)	1966-1968	N.D.-120	Manigold and Schulze (1969)
Surface Waters of United States	1967-1968		Lichtenberg, et al. (1970)
Region:			
Northeast		N.D.-30	
Middle Atlantic		N.D.-30	
Southeast		N.D.-60	
Ohio Basin		N.D.-5	
Great Lakes		N.D.-270	
Missouri Basin		N.D.-840	
South Central		N.D.-110	
Southwest		N.D.-30	
Northwest		N.D.-20	
Iowa Rivers (USA)	1968-1970	N.D.-23	Johnson and Morris (1972)
Aransas Bay, Texas (USA)	1969	N.D.-100	Fay and Newland (1972)
Big Creek, Ontario, Canada	1970	3-67	Miles and Harris (1971)
Seawater, California Current System	1970	2-6	Cox (1971)
Hawaii:			
potable waters	1971	ca 1	Bevenue, et al. (1972)
marine waters	1970-1971	1-82	Bevenue, et al. (1972)
Rivers, Southern California Bight area	1971-1972	120-880	SCCWRP (1972)

sure. These calculations were for direct exposure from water intake and do not account for bioconcentration effects. In 1976, the U.S. EPA recommended that water levels not exceed 0.001 µg/l on the basis of bioaccumulation in food and adverse effects in birds.

According to Lichtenberg, et al. (1970), fresh water entering treatment plants contained DDT residues in amounts 1/10 to 1/500 of the permissible levels for public water supplies as described in the Water Quality Criteria (Fed. Water Pollut. Control Adm. 1968) of 50 ppt.

Assuming an average daily intake of 2 liters of water per individual, Huang (1972) concluded that the maximum daily ingestion would be 0.002 mg DDT, which is based on the highest recorded levels in water. This would amount to approximately 5 percent of the total daily dietary intake. The preponderance of evidence indicates that DDT residues in drinking water are 1 to 3 orders of magnitude less; therefore, it has been concluded that recorded DDT residues have little significance when evaluating DDT effects on animal populations, but may contribute to bioconcentration in aquatic species and higher organisms in the food chain (Woodwell, et al. 1967).

Ingestion from Food

The accumulation of DDT in different species of widely different phylla has made it the classical compound for study of biological magnification of pesticides. An abundance of literature attests to the widespread movement of persistent residues along food chains in natural environments coupled with the biological concentration of the residue at each trophic level. Magnification of DDT occurs by two routes: (1) direct absorption from contaminated water for aquatic organisms, (2) transfer of residues through sequential predator feeding.

Non-target species, such as predatory birds, have been severely affected through reproductive loss due to eggshell thinning. Although in no way comprehensive, the following selected papers illustrate the relative magnitude of bioconcentration of DDT. Johnson, et al. (1971) introduced ^{14}C-labeled DDT into fresh water; within 3 days from initial exposure, the magnification factor in 2 groups of invertebrates (Cladocera and Diptera) ranged over 100,000 times; in two others (Amphipoda and Ephemeroptera), in excesss of 20,000; and in Decapoda and Odonata, up to 3000 magnification. Cope (1971) calculated the accumulation of DDT in comparison to water for several species. It was 70,000 times for oysters, 1,000,000 times for coho salmon, and 1200 to 317,000 in other fish. As a final example of bioconcentration, Woodwell, et al. (1967) measured DDT residues in a Long Island marsh area and observed the following ppm on a whole body wet weight basis: for plankton, 0.04; water plants, 0.08; snail, 0.26; shrimp, 0.16; minnow, 0.94; bill fish, 2.07; heron, 3.5; cormorant, 26.4; gull, up to 75.5.

The primary route of human exposure to DDT is from ingestion of small amounts in the diet. These residues are transferred from agricultural soils, of which 5 percent of the total area has been heavily treated and has an estimated average content of 2 ppm (Edwards, 1966). Since the half-life of DDT is approximately 3 to 10 years (Menzie, 1972) and sandy soils can retain 39 percent at 17 years

(Nash and Woolson, 1967), the presence of DDT residues in foodstuffs derived from contaminated soils will continue for some time.

Monitoring programs by the FDA have been conducted in 80 markets nationwide in the period from 1965 to 1970 and the results are shown in Table 2 (Bevenue, 1976). Meats, fish, poultry and dairy products are the primary sources of DDT residues.

As seen from these data, there have been continual decreases in the overall levels of residues in all classes from 1965 to 1970. Between 1970 and 1973, a significant drop in residues of DDT and DDD occurred, constituting decreases of 86 and 89 percent respectively. DDE decreased only 27 percent. These decreases are reflected in the changing amounts of estimated dietary intake: 1965 - 0.062 mg/man/day, 1970 - 0.024 mg/man/day, 1973 - 0.008 mg/man/day (U.S. EPA, 1975). This trend continued through 1977 as reported by Johnson and Manske (1977). Compared to 49 percent of the samples presently containing organochlorine residues, 54 percent were observed in 1971. DDE in meat, fish and poultry has declined from 0.114 to 0.033 ppm, and in dairy products from 0.043 to 0.017 ppm, while DDT remained constant in meat residues at 0.017 ppm. The decreases in pesticide residues in various food classes indicate that the ban on DDT has indeed lowered the exposure of humans in the diet. This decrease is paralleled by a lowering of the total DDT equivalent in human tissues for the U.S. population average from approximately 8 ppm to 5 ppm residue in fat from 1971 through 1974.

TABLE 2

DDT and Metabolite Residues in Food and Feed*
(Duggan, et al. 1967; Duggan, 1968; Corneliussen, 1969, 1970, and 1972)

Product and time period	Residue (ppm)			
	DDT	TDE	DDE	Total
Dairy products (fat basis, 8-13% fat)				
1965-1966	0.040	0.015	0.075	0.130
1967-1968	0.030	0.019	0.063	0.112
1968-1969	0.023	0.012	0.048	0.083
1969-1970	0.017	0.005	0.043	0.065
Meat, fish, and poultry (fat basis, 17-23% fat)				
1965-1966	0.299	0.139	0.254	0.602
1967-1968	0.103	0.062	0.116	0.281
1968-1969	0.101	0.043	0.100	0.244
1969-1970	0.072	0.049	0.114	0.235
Grains				
1965-1966	0.008	0.002	0.001	0.011
1967-1968	0.004	0.001	0.002	0.007
1968-1969	0.005	0.001	0.001	0.007
1969-1970	0.004	0.001	0.001	0.006
Leafy vegetables				
1965-1966	0.012	0.016	0.005	0.033
1967-1968	0.015	0.007	0.004	0.026
1968-1969	0.010	0.001	0.007	0.018
1969-1970	0.007	0.001	0.002	0.010
Garden fruits (tomatoes, cucumbers, squash, etc.)				
1965-1966	0.027	0.017	0.005	0.049
1967-1968	0.029	0.015	0.002	0.046
1968-1969	0.028	0.012	0.002	0.042
1969-1970	0.019	0.016	0.002	0.037
Fruits				
1965-1966	0.009	0.003	0.002	0.014
1967-1968	0.009	0.001	0.002	0.012
1968-1969	0.009	0.004	0.001	0.014
1969-1970	0.021	0.001	0.001	0.023
Oils (salad oil, margarine, peanut butter, etc.)				
1965-1966	0.009	0.016	0.005	0.030
1967-1968	0.009	0.028	0.018	0.055
1968-1969	0.003	0.003	0.003	0.009
1969-1970	0.006	0.003	0.002	0.010

*Bevenue, 1976

The acceptable daily intake of DDT established by WHO/FAO is 0.005 mg/kg/day. Duggan and Corneliussen (1972) reported the six-year average from 1965 through 1970 in the U.S. diet of DDT and its metabolites to be almost tenfold less at 0.0007 mg/kg/day.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

Measured bioconcentration factors for DDT have been obtained with many aquatic species, both in laboratory tests and from field exposures, but only the species for which the percent lipids could be estimated are used herein. Many of the BCF values include metabolites of DDT, such as DDE.

Species	BCF	Percent Lipids	Adjusted BCF	Reference
Freshwater fish				
Alewife, *Alosa pseudoharengus*	1,296,666	10.	298,000	Reinert, 1970
Lake herring, *Coregonus artedi*	2,236,666	3.3	156,000	Reinert, 1970
Lake whitefish, *Coregonus clupeaformis*	260,000	7.6	78,700	Reinert, 1970
Bloater, *Coregonus hoyi*	2,870,000	20.	330,000	Reinert, 1970
Cisco, *Coregonus sp.*	368,777	6.4	133,000	Miles, & Harris 1970
Rainbow trout, *Salmo gairdneri*	11,607	1.0	26,700	Miles & Harris, 1970
Rainbow trout, *Salmo gairdneri*	38,642	12	7,400	Reinert, et al., 1974
Brown trout, *Salmo trutta*	45,357	1.8	58,000	Miles & Harris, 1973
Lake trout, *Salvelinus namaycush*	458,259	4.4	240,000	Miles & Harris, 1973
Lake trout, *Salvelinus namaycush*	1,168,333	10	269,000	Reinert, 1970

Species	BCF	Percent Lipids	Adjusted BCF	Reference
American smelt, *Osmerus mordax*	770,000	3.9	454,000	Reinert, 1970
Carp, *Cyprinus carpio*	640,000	6.2	237,000	Reinert, 1970
Fathead minnow, *Pimephales promelas*	99,000	8.0	28,000	Jarvinen, et al. 1977
White sucker, *Catostomus commersoni*	110,000	2.8	90,000	Miles & Harris, 1973
Rock bass, *Ambloplites rupestris*	17,500	4.0	10,000	Miles & Harris, 1973
Bluegill, *Lepomis macrochirus*	16,071	4.0	9,200	Mules & Harris, 1973
Yellow perch, *Perca flavescens*	1,073,333	7.9	312,000	Reinert, 1970
Saltwater bivalve molluscs				
Hard clam, *Mercenaria mercenaria*	8,400	1.4	13,800	Woodwell, et al. 1967
Eastern oyster, *Crassostrea virginica*	42,200	1.5	64,700	Lowe, et al. 1971
Eastern oyster, *Crassostrea virginica*	76,300	1.5	117,000	Lowe, et al. 1971
Saltwater decapods				
Pink shrimp, *Penaeus duorarum*	1,200	1.1	2,500	Nimmo, et al. 1970
Shrimp, species not given	3,200	1.1	6,700	Woodwell, et al. 1967
Market crab, *Cancer magister*	14,250	1.3	25,000	Earnest & Benville, 1971
Market crab, *Cancer magister*	4,750	1.3	8,400	Earnest & Benville, 1971
Saltwater fish				
Sheepshead minnow, *Cyprinodon variegatus*	18,800	5.0	8,600	Woodwell, et al. 1967

Species	BCF	Percent Lipids	Adjusted BCF	Reference
Shiner perch, *Cymatogaster aggregata*	43,250	3.4	29,000	Earnest & Benville, 1971
Shiner perch, *Cymatogaster aggregata*	34,750	3.4	23,500	Earnest & Benville, 1971
Dwarf perch, *Micrometrus minimus*	46,500	6.4	16,700	Earnest & Benville, 1971
Dwarf perch, *Micrometrus minimus*	37,000	6.4	13,300	Earnest & Benville, 1971
White perch, *Phanerodon fureatus*	22,250	2.8	18,300	Earnest & Benville, 1971
White perch, *Phanerodon fureatus*	29,250	2.8	24,000	Earnest & Benville, 1971
Pile perch, *Racochilus vacca*	26,750	4.4	14,000	Earnest & Benville, 1971
Pile perch, *Raccochilus vacca*	32,500	4.4	17,000	Earnest & Benville, 1971
Staghorn sculpin, *Leptocotlus armatus*	17,000	1.9	27,000	Earnest & Benville, 1971
Staghorn sculpin, *Leptocotlus armatus*	22,250	1.9	27,000	Earnest & Benville, 1971
Summer flounder, *Paralichthys dentatus*	25,600	0.9	65,400	Woodwell, et al. 1967
Speckled sanddab, *Citharichthys stigmaeus*	15,250	2.7	13,000	Earnest & Benville, 1971
Speckled sanddab, *Citharichthys stigmaeus*	12,250	2.7	10,400	Earnest & Benville, 1971
English sole, *Parophrys vetulus*	20,000	2.0	23,000	Earnest & Benville, 1971
English sole, *Parophrys vetulus*	13,000	2.0	15,000	Earnest & Benville, 1971
Starry flounder, *Platichthys stellatus*	24,750	2.5	22,800	Earnest & Benville, 1971
Starry flounder, *Platichthys stellatus*	23,750	2.5	21,800	Earnest & Benville, 1971

Each of these measured BCF's was adjusted from the percent lipids of the species to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. The geometric mean was obtained for each species, and then for all species. Thus the mean bioconcentration factor for DDT and the edible portion of all aquatic organisms consumed by Americans is calculated to be 39,000.

Inhalation

Levels of DDT found in the air are far below levels that add significantly to total human intake. Stanley, et al. (1971) sampled air in 9 localities in both urban and agricultural areas in the U.S. p,p'-DDT was found in all localities in ranges from 1 ng/m^3 of air to 2520 ng/m^3. Generally, levels were highest in southern agricultural areas and lower in urban areas. These samples were taken during time of high usage of DDT. Most likely, air concentrations are much lower today. Kraybill (1969) estimated the concentration of DDT in the air to be 0.2 ng/m^3 which is in the lower range of Stanley's reported values.

In a study on plant workers, Wolfe and Armstrong (1971) estimated respiratory exposure from the contamination of filter pads placed within respirators. The highest exposures reported were 33.8 mg/man/hour for the bagging operation, with a mean 14.11 mg/man/hour. The authors concluded that workers in fomulating plants not wearing respirators have significant intake of DDT via inhalation. Wolfe, et al. (1967) used a similar method to determine inhalation exposure and found for airplane flaggers in dusting operations 0.1 to 0.2 mg/man/hour levels.

Dermal

Absorption of DDT through skin is minimal. Several factors can influence the rate of absorption, such as the condition of the skin or external factors such as temperature. Technical DDT was less toxic dermally to white rats than a large percentage of other pesticides tested by Gaines (1969). In Wolfe and Armstrong's study (1971), most of the exposure was dermal with the exposure ranging from 5 to 993 mg/man/hour, but these high values did not correlate with significant increases above the general population in the urine of the workers. This led them to conclude that there was a minimal absorption of DDT in exposed skin areas.

Hayes (1966) estimated the intake of DDT to be in the following proportions: food - 0.04 mg/man/day, water -4.6 x 10^{-5} mg/man/day, and air - 9 x 10^{-6} mg/man/day. Wessel (1972) calculated the daily dietary intake of DDT and analogues to be 0.027 DDT, 0.018 DDE and 0.012 ppm DDD. Kraybill (1969) estimated DDT dietary intake to be approximately 85 percent of the total exposure of 30 mg/year. Aerosols, dust and cosmetic exposure were estimated as 5 mg/year, with air and water intakes of 0.03 and 0.01 mg/year, respectively.

From these estimates, it is concluded that the maximum total intake of DDT and analogues does not exceed 0.1 mg/man/day and is probably today considerably less, due to restriction in its use. Since dermal, inhalation and water intake account for less than 10 percent of the total dosage, and in most recent estimates dietary intakes are 0.008 mg/man/day, the actual total dose per day is estimated to be approximately 0.01 mg/man/day or 3.65 mg/year.

PHARMACOKINETICS

Absorption

DDT and DDE are absorbed from the gastrointestinal tract with high efficiency characteristic of dietary fat. Maximum lipid solubilities reach 100,000 ppm. Inasmuch as DDT and metabolites ingested are contained primarily in fat-bearing foodstuffs, such as dairy products, meat and poultry, the absorption of dietary DDT approaches the 95 percent absorptive values for these dietary fats. Over 65 percent of labeled DDT and metabolites were found in the nine-day bile collections of treated rats (Jensen, et al. 1957).

Determinations of absorption and assimilation of ingested DDT in humans have been studied by following the serum concentrations of the compound after ingestion (Morgan and Roan, 1971). Highest concentrations were found in the samples taken 3 hours after ingestion of DDT. Serum concentrations remained above pre-dose level for at least 14 hours but returned to base level within 24 hours. Blood levels show a relatively slow uptake and assimilation consistent with physiological dependence on intestinal fat absorption. However, absorption proceeded faster than transport out of the vascular compartment into tissue storage with a dosage of 20 mg. Assimilation of the entire given dose was completed within 24 hours. One subject ingested 2.82 g technical DDT, with approximately 85 percent being stored or excreted in the urine. The authors concluded that several factors collectively cause storage values to underestimate absorptive efficiency and that true intestinal absorption of DDT in man is essentially similar to fat.

Distribution

DDT and its metabolites have been found in virtually all body tissues, approximately in proportion to respective tissue content of extractable tissue lipid, except in the brain. Adipose/blood ratios of DDT have been variously estimated from 140 to 1000; more recent estimations indicate that the ratio is approximately 280 fat: plasma (Morgan and Roan, 1977). This ratio represents a dynamic equilibrium between DDT in plasma lipoprotein and in triglycerides stored in fat cells.

Long-term admininstration of DDT to mice and its storage in various tissues have been reported by Tomatis, et al. (1971). Apart from o,p'-DDT, there is direct relationship between the concentration of each metabolite in each organ and the dose to which the animal was exposed. The highest concentration of DDT and metabolites was found in fat tissue, followed by reproductive organs, liver and kidney together, and lastly, brain. The most prevalent stored compound was unaltered p,p'-DDT. Storage levels of o,p'-DDT were proportionally higher in animals receiving the control diet or exposed to the lowest DDT dose. In the reproductive organs and fat, females had considerably greater levels of all three compounds than males, with no storage differences in kidney, brain and liver.

In Rhesus monkeys, Durham, et al. (1963) noted that dosage levels from .25 to 10 mg/kg/day technical DDT in the diet produced a maximum storage in fat by 6 months, which was not increased by feeding for an additional period of 7 years. Of interest is the fact that no DDE was detected in the fat of these monkeys. However, high levels of DDE storage were found in monkeys fed DDE, indicating an inability to convert DDT to DDE.

Human adipose storage decreases in the order DDE > p,p'-DDT > DDD. Serum and adipose concentrations of DDE rise slowly to DDT ingestion with the peak some months following termination of dosing. In contrast, levels of DDT, DDD and o,p'-DDT decline more rapidly. Fitted exponential curves in man suggest that 25 percent of stored material should be lost within a year after the last administration. Elimination of very low levels from storage of DDT proceeds much more slowly than disposition of the large stores of DDT accumulated by occupationally exposed or dosed volunteers. Thus, when DDT in fat amounts to 100 ppm, the chemical is lost at a rate of 4.1 mg/day or 0.24 percent of the total store. When, after 2 years, the load has decreased to 40 ppm, the loss rate falls to 0.2 mg/day or 0.10 percent of store; projected to 5 ppm, storage loss is 0.03 mg/day DDT or only 0.04 percent of body stores (Morgan and Roan, 1971).

Hayes, et al. (1971) have shown that subjects ingesting high doses up to 35 mg/kg/day DDT reach a storage plateau sometime between 18 to 22 months (Figure 1). Volunteers had mean adipose concentrations of 281 ppm with a high of 619 over a 21-month period. DDE reached levels as high as 71 ppm with a mean of 25.8 ppm in 21 months, but the values increased during recovery to a peak of 563 ppm approximately two years after dosing, and fell only slightly to 50.8 after a 3-year recovery. Over a 5-year recovery period,

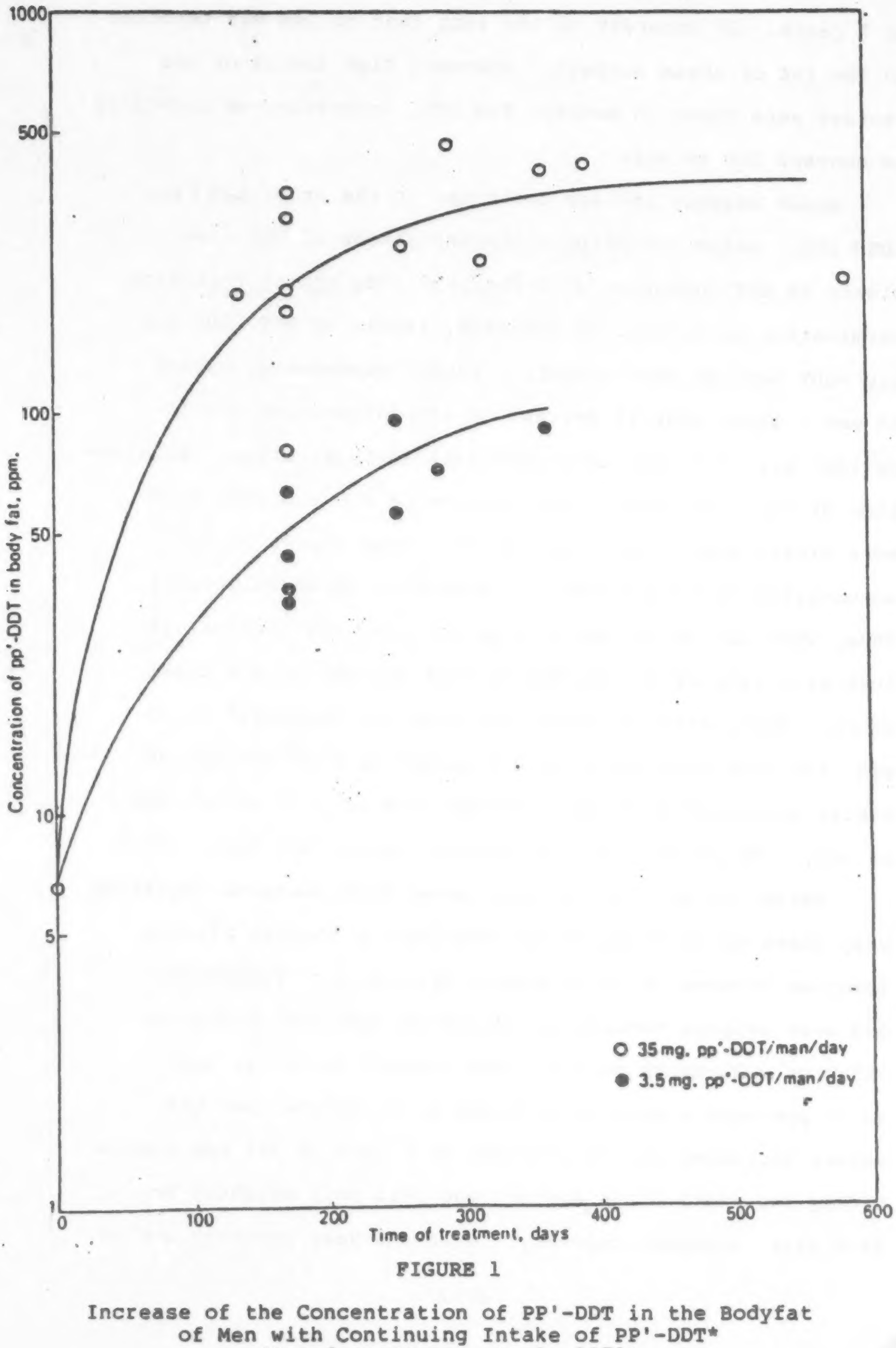


FIGURE 1

Increase of the Concentration of PP'-DDT in the Bodyfat of Men with Continuing Intake of PP'-DDT*
(Based on Hayes, et al. 1971)

the concentration of DDE in fat as a percentage of all DDT derived material rose from 26 to 47 percent.

The preceding data are consistent with the known fact that DDE is very slowly eliminated from the body and has the higher affinity for storage. The average North American adult, with 17 kg of body fat, contains approximately 25 mg of DDT and 75 mg of DDE. Storage loss data predict that, if dietary intake were eliminated, most of the DDT would be lost within one or two decades, but DDE would require an entire lifespan.

It has been suggested by a number of investigators that DDT levels reflect recent exposure to DDT, while DDE levels correlate well with long-term exposure and storage capacity of the human body (Roan and Morgan, 1971; Edmundson, et al. 1969b). In occupationally exposed workers, Laws, et al. (1967) determined the concentrations in fat of DDE expressed as DDT to be 25 to 63 percent of total DDT related material. This is in contrast with 72 to 92 percent found in the general population.

Tissue storages of DDE in the general population originate almost entirely from dietary DDE rather than DDT converson (Roan and Morgan, 1971).

A comparison of DDT and DDE storage in the U.S population is shown in Table 3 (U.S. EPA, 1975). Mean levels of DDT in human adipose tissue show a downward trend from 7.95 ppm in 1971 to 5.89 ppm in 1973. Overall DDE levels on the other hand, do not show a similar trend; and long-term storage is reflected in the slightly increased percentage of the total DDT found as DDE.

TABLE 3

National Summary of Total DDT Equivalent Residues in Human Adipose Tissue*
(Total US Population Basis)

	FY 1970	FY 1971	FY 1972	FY 1973
Sample size	1,412	1,616	1,916	1,092
Frequency	99.3%	99.75%	99.95%	100.00%
Geometric mean	7.87 ppm	7.95 ppm	6.88 ppm	5.89 ppm
Percent DDT found as DDE	77.15%	79.71%	80.33%	81.19%

Total DDT equivalent = (o,p'-DDT + p,p'-DDT)
+ 1.114 (o,p'-DDD + p,p'-DDD +
p,p'-DDE + o,p'-DDE)

*U.S. EPA, 1975

A simple linear model has been developed by Durham, et al. (1965b) to describe the relationship between the concentration of DDT in the body fat of man and the daily dose of this compound. The equation is: $\log C_1 = 0.7 \log I + 1.3$, where C_1 is the fat storage of DDT in ppm and I is the DDT intake in mg/man/day. This equation gives good agreement with storage found by other investigators and is represented in graphical form in Figure 2.

At high levels of exposure, human volunteers have demonstrated a steady state of storage or plateau which is exponentially approached within 18 months. This plateau level is proportional to the dose administered (Figure 1).

Metabolism

The metabolism of DDT has been well established in several mammalian species. Generally, two separate reductive pathways produce the primary endpoint metabolites, DDE and DDA. As seen in Figure 3, a generalized outline of the metabolism of DDT, the predominant conversion is of DDT to DDD via dechlorination. This is the first product in a series which results in metabolites which are later excreted. The other primary pathway proceeds via reductive dehydrochlorination which results in the formation of DDE, the major storage product in animals and humans.

Peterson and Robison (1964) showed convincingly that DDD was the intermediate metabolite leading to DDA. Adult male rats were treated acutely by gavage with 100 mg/kg purified DDT and sacrificed 4 to 60 hours later. Liver samples yielded primarily DDT and DDD, in a ratio of 14:1.

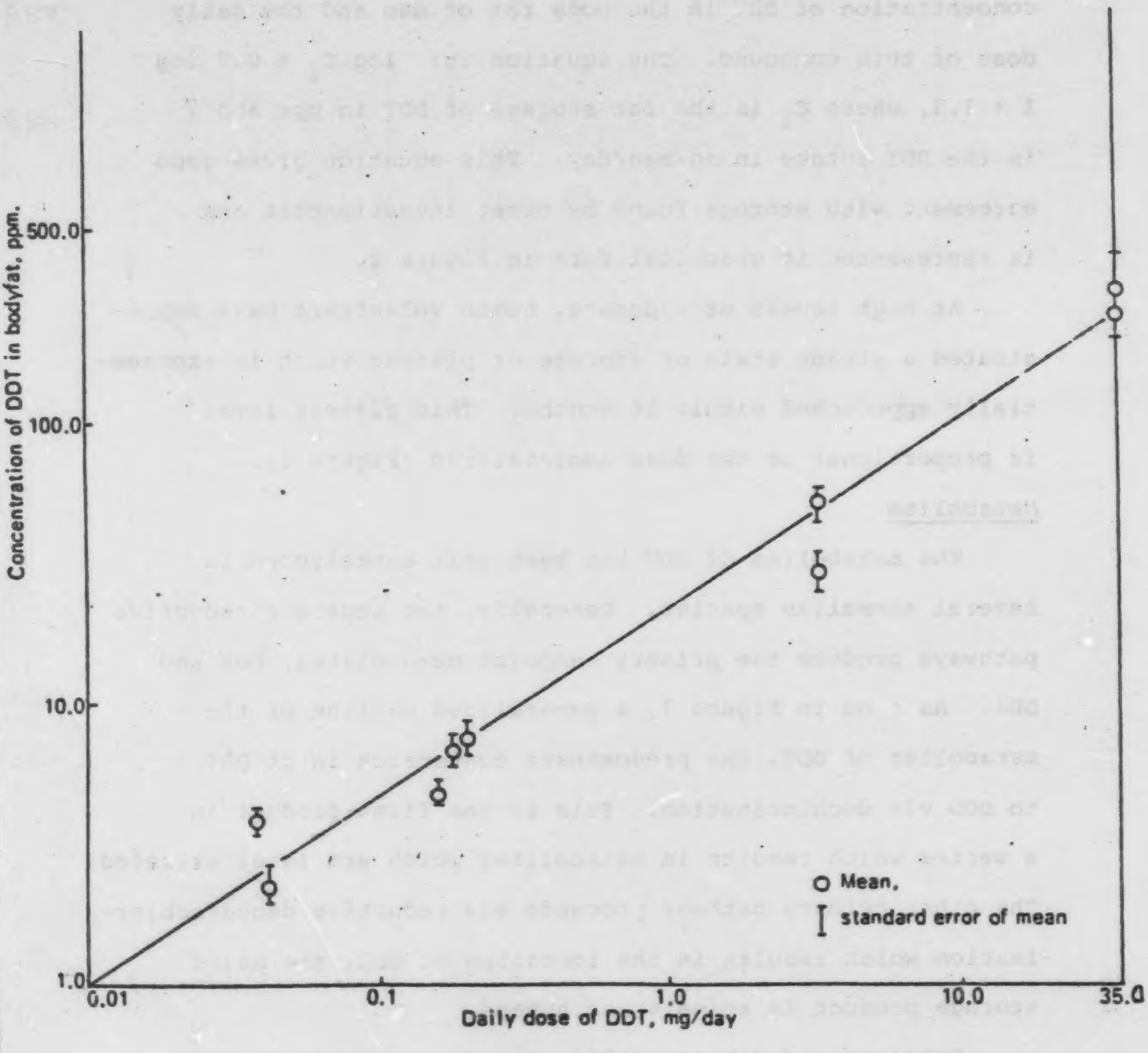


FIGURE 2

Relationship Between the Concentration of DDT in the Bodyfat of Man and the Daily Dose of that Compound*
(Based on Hayes, et al. 1971 and Durham, et al. 1965b)

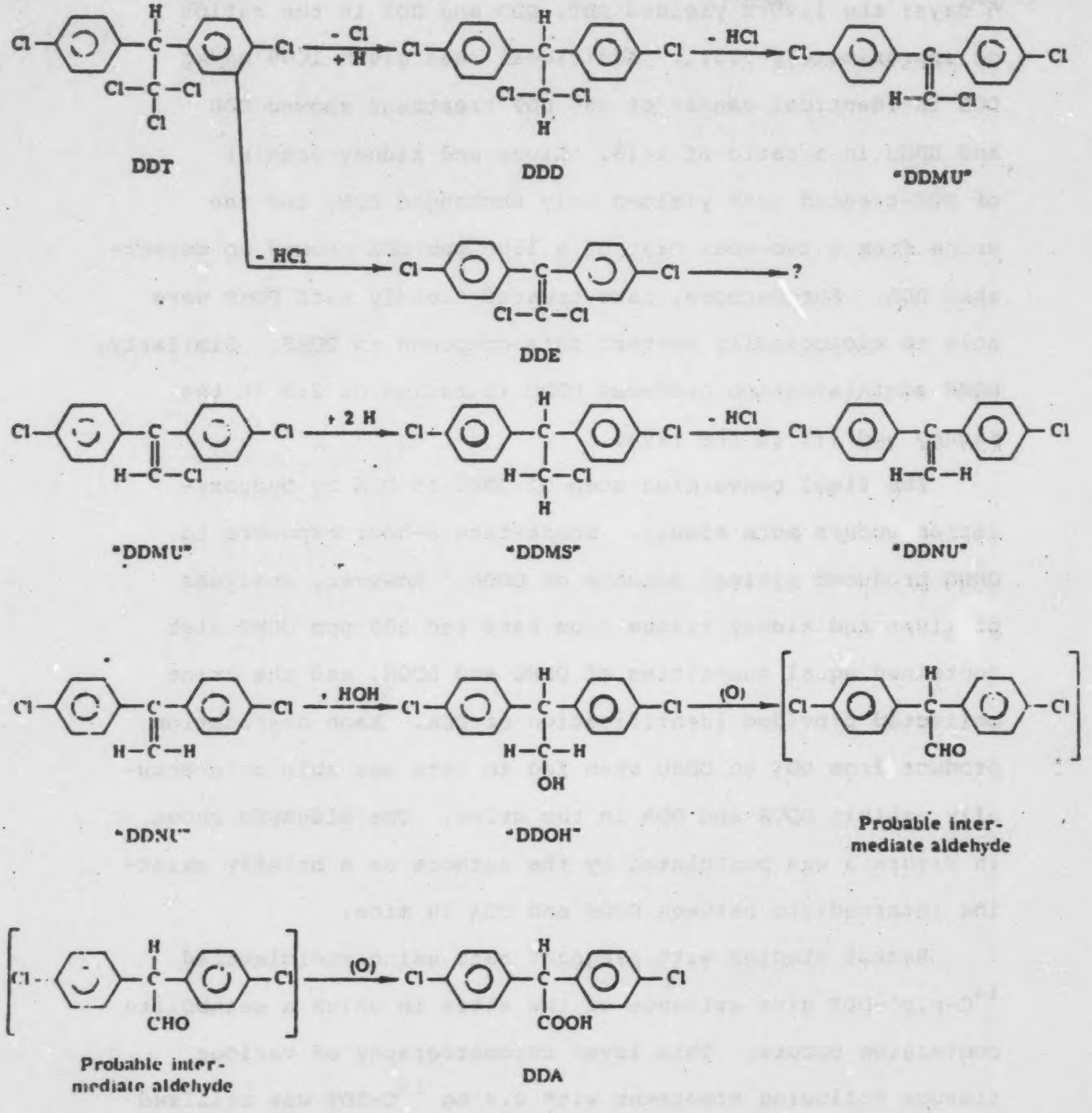

- Cl
+ H
- HCl
DDT
DDD
"DDMU"
- HCl
?
DDE
+ 2 H
- HCl
"DDMU"
"DDMS"
"DDNU"
+ HOH
(O)
"DDNU"
"DDOH"
Probable intermediate aldehyde
(O)
Probable intermediate aldehyde
DDA

FIGURE 3

Metabolic Products of P,P'-DDT in the Rat (Peterson and Robison, 1964)

Rats fed a diet of 1500 ppm purified DDT were sampled at 6 days; the livers yielded DDT, DDD and DDE in the ratios of approximately 3:5:1. Additional rats given 1000 mg/kg DDD in identical manner of the DDT treatment showed DDD and DDMU in a ratio of 1:13. Liver and kidney samples of DDE-treated rats yielded only unchanged DDE, and the urine from a two-week diet of a 1000 ppm DDE showed no detectable DDA. Furthermore, rats treated acutely with DDMU were able to biologically convert this compound to DDMS. Similarly, DDMS administration produced DDNU in ratios of 2:5 in the kidney and 3:1 in the liver.

The final conversion step of DDNU to DDA by hydroxylation occurs more slowly. Short-term 6-hour exposure to DDNU produced minimal amounts of DDOH. However, analyses of liver and kidney tissue from rats fed 500 ppm DDNU diet contained equal quantities of DDNU and DDOH, and the urine collected provided identification of DDA. Each degradation product from DDT to DDNU when fed to rats was able to eventually exhibit DDOH and DDA in the urine. The aldehyde shown in Figure 3 was postulated by the authors as a briefly existing intermediate between DDOH and DDA in mice.

Recent studies with pregnant rats using radiolabeled ^{14}C-p,p'-DDT give evidence of the sites in which a metabolite conversion occurs. Thin layer chromatography of various tissues following treatment with 0.9 mg ^{14}C-DDT was utilized to determine the relative percentages of the metabolites produced. In the liver, from 12 to 24 hours the ratio of DDT, DDD and DDE was unchanged at approximately 3:3:1, a ratio similar to that found by Peterson and Robison (1964) of 3:5:1 in male rats. Liver activity for DDT conversion is much higher in the adults in comparison to neonates. The results for the metabolites recovered from different tissues and fetuses 8 to 10 hours post exposure are shown in Tables 4 and 5 (Fang, et al. 1977). DDE was the major metabolite in all tissues. DDD was a minor metabolite, with the exception of spleen, in which DDD and DDE were equal. DDA was detected in high levels in lung, intestine, kidney and blood, in lower levels in spleen, placenta and fetus; and was undetected in muscle, heart, pancreas and brain. These observations suggest that enzymatic activity for the dehydrochlorination and reductive dechlorination reactions transforming DDT to DDD and DDE are present in all tissues, whereas the enzymes involved in the hydrogenation and hydroxylation steps changing DDD to DDA are absent in brain, heart, pancreas and muscle of the rat.

The metabolism of o,p'-DDT in rats shows no striking differences to that of p,p'-DDT. Feil, et al. (1973) were able to detect 13 different metabolites in the rat excreta by nuclear magnetic resonance spectra. Besides o,p'-DDD and o,p'-DDA, a number of additional ring hydroxylated DDA forms were present. Serine and glycine conjugants and o,p'-dichloro-benz-hydrol were identified in the rat urine. These results indicate that o,p'-DDT is extensively metabolized.

Radiolabeled o,p'-DDD given orally in a 100 mg dose to rats yielded, in both feces and urine, o,p'-DDA, aromatic 3-, 4-monohydroxy and 3, 4-dihydroxy substituted o,p'-DDA. Comparison of urinary excretion of o,p'-DDD metabolites of rats and humans are fundamentally similar. Hydroxylation

TABLE 4

Concentration of ^{14}C-DDT and its Metabolites in the Tissues of Infant Rats after Consumed Milk from Dam Receiving an Oral Dose of 0.9 mg ^{14}C-DDT and of the Dams (ug DDT and Equivalent per g Dry Tissue)

Elapsed time (days)	Stomach content (milk)	Stomach	Blood	Liver	Kidney	Intestine	Lung	Heart	Brain	Carcass
					Infant Rats					
1(4)[a]	15.26±3.27[b]	4.82	.72±.34	13.93±2.50	2.50± .53	13.64±3.37	3.30± .97	1.21±.22	1.23±.35	6.34±2.22
2(4)	4.56± .46	2.81±.13	1.59±.52	14.23±6.94	4.35± .84	13.48±6.36	5.05±1.60	1.57±.56	2.24±.94	9.11±1.12
3(4)	3.49±1.09	2.31±.06	1.70±.15	12.13±4.26	4.73± .71	11.09±3.72	6.23±1.78	1.91±.64	1.83±.94	10.98±1.63
4(4)	3.73± .35	2.18±.15	1.59±.34	8.29±1.73	3.52±1.23	8.42±2.36	5.25± .75	2.00±.85	1.83±.72	9.64± .57
7(4)	1.62± .18	1.59±.28	1.23±.29	5.96±1.78	3.08± .72	8.07±3.19	4.26± .79	1.13±.26	1.11±.62	7.09± .57
11(2)	1.73	1.42	1.21	5.93	3.13	5.98	4.25	1.81	1.30	6.16
14(3)	0.75	1.03	0.44	4.64	2.22	5.42	1.97	1.04	0.62	4.39
21(2)	1.33	0.99	0.40	2.39	0.76	1.95	1.13	0.60	0.28	2.42
28(2)	0.48	0.70	0	1.11	0.20	0.95	0.52	0.18	0.14	1.87
					Dams					
14	-	-	0	0.68	.07	.20	1.12	.28	.06	-
28(2)	-	-	0	0.50	.12	.78	.40	0	.10	-

[a] Number of neonates used

lues are means ± standard deviation

t al. 1977

TABLE 5

^{14}C-DDT and its Labeled Metabolites in Different Tissues of Pregnant Rats 8 or 10 hr after Receiving an Oral Dose of ^{14}C-DDT

Tissue	Radioactivity recovered (meOH:hexane) (%)	R_F Values				
		.02-.04 DDA	.36-.43 DDD	.46-.52 DDT	.56-.61 DDE	75
Blood	83	26	10	31	33	1
Brain	100	0	18	36	46	0
Fetus	86	8	20	25	35	12
Heart	100	0	10	67	20	3
Intestine	93	39	18	11	31	1
Kidney	88	24	5	24	34	13
Lung	100	41	6	8	32	14
Muscle	99	0	0	9	72	19
Pancreas	100	0	5	15	59	21
Placenta	100	4	9	5	49	27
Spleen	83	11	32	14	36	0

Fang, et al. 1977

occurs primarily at the 3 and 4 positions. Humans show a higher percentage of total dose excreted in the urine than rats, 10 to 50 percent versus 3 to 7 percent. Serine and glycine conjugates are excreted in the urine of man and rat (Reif and Sinsheimer, 1975).

The metabolism of DDT in mouse follows essentially the same pathways as the rat (Gingell and Wallcave, 1976). No species differences in overall rates of metabolism of DDT, as measured by urinary excretion of ^{14}C were observed. Further studies investigating chronic exposure up to 4 months, have demonstrated fundamental differences in the metabolic and physiological handling of DDT among other rodent species. Both Swiss and CF_1 mice produce small but significant amounts of DDE in urine, whereas none was found in hamster urine (Gingell, 1976). With long-term feeding experiences, the mouse increasingly eliminates DDE, and at the termination of the experiment, nearly as much DDE as DDA was found (Gingell and Wallcave, 1976). The authors suggest that DDE may be the proximate hepatotumorigenic metabolite in mice, inasmuch as hamsters are not susceptible to DDT tumorigenesis and do not form DDE. Additionally, hamsters are resistant to toxic effects of DDT up to 2100 mg/kg (Agthe, et al. 1970).

Two major studies by Hayes, et al. (1971) and Roan and Morgan (1977) are the basis for what is known of the metabolism of DDT in man and are here described. Hayes, et al. (1971) performed two studies, exposing volunteers from a U.S. penitentiary to technical or recrystallized p,p'-DDT at rates from 3.5 mg to 35 mg/man/day. In the first study, ten subjects were studied: three for one year at 3.5 mg/man/day and seven for one year at 35 mg/man/day. In the second study, 24 men could be followed for a period of over four years. They consisted of four groups: G1 - a control, whose diet was estimated as having 0.18 mg/man/day DDT; G2 - receiving 3.5 mg technical DDT (85 percent p,p'-DDT); G3 - receiving 35 mg technical DDT (85 percent p,p'-DDT); and G4 - receiving 35 mg recrystallized p,p'-DDT.

Roan, et al. (1971) and Morgan and Roan (1977) measured the concentrations of p,p'-DDE, p,p'-DDD and p,p'-DDA in blood, fat and urine in response to oral dosing with these compounds. Four volunteers ingested technical DDT doses ranging from five to 20 mg/day for up to six months. The total dose ingested ranged from 0.06 g to 2.82 g. Two volunteers ingested a total dose of 0.45 g p,p'-DDE in a three-month period. A single volunteer was used for each dosing of DDD and DDA for total dosages of 0.41 g and 0.105 g, respectively.

From these studies, Morgan and Roan (1977) concluded that the conversion of DDT to DDE occurs with considerable latency. The magnitude of conversion at these levels was estimated to be less than 20 percent conversion in the course of three years. An upper trend in DDT fat storage over this time course may be due to release of stored DDT and further conversion to DDE, but no more than one-fifth of the absorbed DDT ultimately undergoes this conversion. The o,p'-isomer was not found to be present in fat and blood of the subjects. DDE-dosed subjects did not exhibit any significant excretion of p,p'-DDA in excess of predose values. Dose-dependent increases in DDD blood levels with DDT dosing indicated the existence of this metabolic pathway. Urinary

DDA excretion and serum DDD concentrations showed increases with DDT dosage and declined after dosing ended. Conversely, DDE exhibited an upward trend for months after dosing. These facts further support the mutally exclusive role of DDD, rather than DDE, in the formation of the urinary metabolite, DDA. Taken together, these results strongly confirm that the metabolism of DDT in man is identical to the pathways reported by Peterson and Robison (1964) for the mouse. Metabolic conversion of DDT by dechlorination to DDA proceeds more rapidly and accounts for approximately one-fifth of the DDT load, which is excreted in the urine. DDE, or the storage metabolite, is produced from DDT more slowly, via dehydrochlorination, and overall conversion will be approximately 20 percent in three years.

Excretion

Studies were conducted by Wallcave, et al. (1974) on the excretion of DDT metabolites in hamsters and mice. Of the ingested dose of between 22 to 29 mg per animal over a four-month period, 12 to 14 percent was recovered in the urine as DDA or DDE. Steadily increasing amounts of DDE excretion were observed in mice with long-term feeding, whereas the hamster had no DDE present. Approximately 9 percent of ingested DDT was found in fecal excretion as DDD or DDT in mice, as compared to 3 percent in hamsters. These species seem to have less biliary excretion than the rat, in which 65 percent of a DDT dose can be found in the bile collections and large amounts of DDT conjugate are found in the feces (Jensen, et al. 1957).

The excretion of DDT was investigated in human volunteer studies of Hayes, et al. (1971) and Roan, et al. (1971), previously described. Excretion of DDA in the urine increased rapidly in the first few days with a following gradual increase in the subjects dosed with 35 mg/man/day to a steady level of approximately 13 to 16 percent of the daily dose. DDA excretion fell rapidly following cessation of dosing. Since storage levels did not increase after reaching steady state, these volunteers were apparently able to excrete 35 mg/day of the amount they had ingested. This is probably due primarily to excretion of DDT from the gut inasmuch as only 5.7 mg/day of all DDT isomers found in urine. Gut organisms have a demonstrated capacity for degradation of DDT to DDD and DDA and may be important in fecal excretion.

Occupationally exposed workers have been shown to have significantly increased levels of DDA excretion in the urine. Ortelee (1958) classified individuals as heavy, moderate and slight exposure groups in formulating plants and found a good correlation between exposure and DDA in the urine. Laws, et al. (1967) were not able to find DDA in urine samples from all persons of the general population due to insensitivity of analytical methods at the time. In workers, increased levels of DDA excretion were found, but paradoxically, DDE was found in only slightly higher concentrations in exposed workers versus the general population with no correlation with increasing work exposure. Estimations of total intake of DDT based on DDA in urine are in good agreement with estimations of intake based on the calculations of DDT in fat by Durham, et al. (1965a).

Morgan and Roan (1977) have calculated from excretion measurements in disappearance curves the following rank order of loss rates from storage from fastest to slowest: DDA, DDD, o,p'-DDT, p,p'-DDT and p,p'-DDE. Differences in excretability from one end of the scale to the other are very great, water solubility being a possible important variable. Interspecies differences also exist in the capacity for unloading stored DDT. Man, as compared to the rat, dog or monkey, exhibits a considerable slower rate of loss, which may be related to differences in renal handling of the pesticide. If dietary intake were completely eliminated, most of the DDT would be lost in 10 to 20 years but DDE would require almost an entire lifespan for removal.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Acute toxic effects show central nervous system symptoms, such as hyperexcitability, generalized trembling, convulsions and paralysis within five to ten minutes following i.v. administration and a latent period of several hours for oral dosing in experimental animals. LD_{50} for rats typically range from 100 to 400 mg/kg orally and 40 to 60 mg/kg i.v. (Negherbon, 1959; Hayes, 1963). Dermal exposure in rats was toxic at 3000 mg/kg. DDE has an oral LD_{50} in rats of 380 mg/kg in males and 1240 mg/kg in females; DDA, 740 mg/kg in males and 600 mg/kg in females (Hayes, et al. 1965). The oral LD_{50} of DDT is 60 to 75 mg/kg in dogs; in rabbits, 250-400 mg/kg; and in mice, 200 mg/kg (Pimentel, 1971).

Studies on acute toxicities in animals indicate that the correlation between pathological symptomatic effect and pesticide level is highest in the brain. Dale, et al. (1963) observed tremors in male rats four hours after administration of DDT, when the brain concentration reached 287 ppm on a lipid basis.

Acute poisoning in man is a rare event and no well-described case of fatal uncomplicated DDT poisoning has been reported. General symptoms are similar to those found in animals and include dizziness, confusion, and most characteristically, tremors. In severe poisoning, convulsions and parasthesia of extremities may intervene.

Single ingestion of 10 mg/kg produces illness in some, but not all, subjects. Smaller doses generally produce no illness. Convulsions and nausea frequently occur in dosages greater than 16 mg/kg. Dosages as high as 285 mg/kg have been taken without fatal result but such large dosages are usually followed promptly by vomiting, so the amount retained is variable (Hayes, 1963).

Although a number of pathological changes have been noted in experimental animals, the most consistent finding in life-time feeding studies has been an increase in the size of liver, kidneys and spleen, extensive degenerative changes in the liver and an increased mortality rate. In rats, Laug, et al. (1950) observed hepatic alteration with feedings in diet at 5 ppm DDT. At dose levels of 600 and 800 ppm, significant decreases in weight gain and increased mortality were observed in rats (Fitzhugh and Nelson, 1947). The observation that increased mortality results from doses above 100 ppm DDT in the diet is well established in mice (Walker, et al. 1972).

In contrast to the rodent models, Rhesus monkeys, fed diets with up to 200 ppm DDT, showed no liver histopathology, decrease in weight gain or food consumption, or clinical signs of illness. Several monkeys fed 5000 ppm in the diet had some weight loss, prior to early death due to DDT poisoning (Durham, et al. 1963). In one animal, liver pathology consistent with DDT poisoning in other animals was found.

No clinical or laboratory evidence of injury to man by repeated exposure to DDT has been reported. Volunteers ingesting up to 35 mg/day for 21 months had no alterations in neurological signs, hematocrit, hemoglobin and white blood cell counts. No changes in cardiovascular status or liver function tests were noted (Hayes, et al. 1971).

Studies of exposed workers by Laws, et al. (1967), Wolfe and Armstrong (1971), Almeida, et al. (1975) have demonstrated no ill-effects from long-term high levels of exposure, as judged by physical examination and chest X-ray.

Furthermore, the dermal toxicity of DDT is practically nil. A few cases of allergenic reaction have been observed, which are probably due to an extreme sensitivity of the individual.

Synergism and/or Antagonism

One of the primary concerns about pesticide residues is the possibility that they may act synergistically with other chemicals over a long period to produce cancer. The accumulation and summation of carcinogenic exposure from various sources may present a health problem of great significance.

DDT, a strong inducer in the mixed function oxidase system, potentially could enhance the biological effects of other chemicals by activation, or diminish their activities through detoxification mechanisms. Weisburger and Weisburger (1968) were able to enhance the incidence of hepatomas in rats caused by N-fluorenacetamide (2-AAF) by co-administration of DDT. They had previously shown that 2AAF is metabolized by a mixed function oxidase system to the hydroxy intermediate which is carcinogenic. By stimulating liver metabolism with 10 mg/day DDT which, by itself, causes no hepatomas, the percentage of animals bearing tumors from a dose of 1 mg/day 2-AAF for up to 52 weeks rose from 67 to 90 percent in males and from 7 to 33 percent in females.

Conney (1967) observed decreases in phenobarbital induced sleeping times proportional to the dose of DDT given to rats two days earlier. Doses of 1 and 2 mg/kg of body fat caused a 25 and 50 percent reduction in sleeping time, respectively. This response is due to the greater capacity of the MFO system to detoxify phenobarbital to a more readily excretable form. Similar effects have been seen for Librium, methyprylon and meprobamate in rats (Datta and Nelson, 1968).

Enhancement of metabolic activity has been demonstrated in workers occupationally exposed to several insecticides, DDT included (Kolmodin, et al. 1969). In these workers, the half-life of antipyrine was significantly decreased in comparison to controls.

Deichmann, et al. (1967) evaluated the synergistic effects of aramite (200 ppm), DDT (200 ppm), methoxychlor (1000 ppm), thiourea (50 ppm) and aldrin (5 ppm) given singly or in combination to rats. These dosages were approximately 50 percent of the levels reported to induce liver tumors. Rats fed combinations of aramite, DDT, methoxychlor and thiourea, with a total tumorigenic dose of 200 percent had a 17 percent tumor incidence. Similarly, a combination of aramite, DDT, methoxychlor and aldrin had a 10 percent tumor incidence. Single chemical feedings had the following incidences of tumors: aramite - 23 percent; DDT - 17 percent; methoxychlor - 18 percent; thiourea - 28 percent; and aldrin - 25 percent. Control rats had 23 percent tumors. Since both total tumors and liver tumors were essentially the same in control versus experimental groups, those authors concluded that the compounds did not act in an additive manner and further suggested that the mixtures might have an antagonistic effect in the reduction of tumors below control.

Walker, et al. (1972) produced liver tumors in mice with either 100 ppm DDT or 5 ppm dieldrin. Two types of histology were scored: simple nodular growth of parenchymal cells (A), and papilliform adenoid growth of tumor cells (B). Combination of the two chemicals showed an overall increase in tumor numbers in males only, 53 to 88, when compared to 100 ppm DDT alone. What is most striking, however, is that for both males and females, there was a significant shift in proportion to the more tumorigenic type B phenotype with the combined feeding.

The induction of the hepatic enzymes occurs in animal models and possibly in occupationally exposed workers, as shown by increased drug metabolism. However, the tumorigenicity data present inconsistent findings with respect to activation or detoxification, depending on the agent used. This is not an uncommon paradox when dealing with metabolic induction. The effects on human health as a result of low level exposure and synergistic/antagonistic interactions with other chemicals are unknown.

Teratogenicity

Minimal teratogenic effects have been reported following high acute dosages. Hart, et al. (1971) showed that DDT has an effect on prematurity and causes an increase in the number of fetal resorptions in rabbits given 50 mg/kg on days 7, 8 and 9 of gestation. In the experimental group, 25 percent of the implantations suffered reabsorption *in utero* in comparison to 2 percent in the control. The weight of the viable fetuses was significantly lower in the treated animals. The dose used in the experiment corresponds to 1/6 to 1/10 of the acute LD_{50} for the species.

Low level exposure to DDT exerts an adverse effect on reproduction of several avian species. While data for mammalian species are meager, published reports to date indicate that dietary intake has little or no effect on the reproductive success of laboratory animals. Dietary DDT at 7 ppm was fed to BALB/C and CFW strains of Swiss mice for 30 days prior and 90 days post-breeding. In the BALB/C strains, there was a slight reduction in overall fertility, but fecundity (litter size) was greater than control values. With the CFW strain, no differences in fertility or fecundity were noted (Ware and Good, 1967).

Ottoboni (1969) studied the effect of DDT at levels of 0, 20 and 200 ppm on fertility, fecundity, neonatal morbidity, and mortality through two successive generations in

Sprague-Dawley rats. No alteration in sex ratios nor any evidence of teratogenic effect was found among live or stillborn young. Litter size, weights at birth and weaning showed no differences between treated and control. Poor survival of the young to weaning pups in the 200 ppm group was observed. This finding was compromised by large losses in the control, yet the 20 ppm diet group was unaffected. Viability of young was high for all three groups in the F_1 generation breedings. Of the other indices studied, fecundity, fertility and mortality, none was significantly affected. The only significant finding was an increase in ring tail, a constriction of the tail followed by amputation, in the offspring of mothers whose diets contained 200 ppm DDT.

Krause, et al. (1975) noted a damaging effect on spermatogenesis in rats which was somewhat persistent for 90 days, and fertility was markedly reduced. This followed acute 500 mg/kg dose on days 4 and 5 of life or 200 mg/kg from day 4 to day 23. In this experiment the administered dosages are close to the LD_{50} for the species; therefore, these results cannot be considered conclusive, since acute toxicity will alter other physiological parameters that could affect fertility.

Both p,p'-DDT and o,p'-DDT have been shown to possess estrogenic activity in rodents and birds (Welch, et al. 1969; Bittman, et al. 1968). Increases in uterine wet weight, and uptake of labeled glucose into various precursors which are in competition with estrodiol 17B for uterine binding sites have been demonstrated.

The importance of the estrogenic activity of low level DDT exposure is difficult to estimate. Since fertility in the mammalian female and male is dependent upon complex hormonal interactions, chemical interference may represent a hazard. As an example, Ottoboni (1969) suggested that 20 ppm of DDT in the diet had an adverse effect on the sub-fertile females in reproductive prime and observed a greater fertility or protective effect in aging female rats as compared to controls. In a later study by Wrenn, et al. (1970) long-term feeding of o,p'-DDT to rats did not interfere with normal reproduction nor were estrogen sensitive physiological parameters significantly affected.

Mutagenicity

DDT has not shown mutagenic activity in any of the bacterial test systems thus far studied. McCann, et al. (1975) found no increased frequency of reversions in Salmonella typhimurium strains TA-1535, 1537, 98 or 100 with 4 ug/plate DDT. In addition, DDE was nonmutagenic in this system; neither DDT nor DDE were positive with S-9 microsomal activation. Marshall, et al. (1976) confirmed these studies with doses up to 2500 µg/plate DDT and 1000 µg/plate DDE. No inhibition of growth was seen in the E. coli Pol-A strains with 500 µg of DDT and the metabolites DDD and DDE (Fluck, et al. 1976). DDT was also negative in the rec-assy with Bacillus subtilis (Shirasu, et al. 1976).

Fahrig (1974) reviewed the activity of DDT and its metabolites DDE, DDD, DDOH and DDA in several other bacterial systems. All metabolites were negative, as judged by resistance to 5-methyltrptophane and streptomycin in liquid holding tests. Back mutation to prototrophy was negative in two strains of Escherichia marcescens, and was negative to galactose prototrophy in E. coli.

The only positive result found in any of the bacterial test systems was reported by Buselmaier, et al. (1972) upon the administration of DDD to mice and assaying for back mutation of Salmonella typhimurium and E. marcescens following incubation in the peritonium in the host-mediated assay. However, DDT, DDE and DDA were found negative by this method.

In summary, with the exception of one metabolite -DDD - in the host-mediated assay, no genetic activity has been detected in the prokaryotic test systems.

Tests on eukaryotic yeast cells have been uniformly negative. Fahrig (1974) investigated the effect of DDT and various metabolites on mitotic gene conversion in Saccharomyces cerevisiae, which detects single strand breaks of the DNA. Host-mediated studies with DDT, DDD and DDE of cells incubated in testis, liver and lung of rats were also negative. Clark (1974) found no significant increases in mutagenicity of conidia of Neurospora crassa incubated in vitro and in vivo with the host-mediated assay.

Vogel (1972) measured X-linked recessive lethal mutations in Drosophila melanogaster and found activity for DDT and DDA, with negative results for DDE, DDD and DDOH.

Clark (1974) examined the relationship between spermatogenesis stages in D. melanogaster and the effect of DDT on dominant lethality and chromosome abnormalities. Sequential breedings of the treated males with virgin females at three day intervals indicated that DDT causes an increase in dominant lethality in early spermatid and spermatocyte stages. This increased lethal effect was correlated with an increase in non-disjunction.

In mammalian systems, the mutagenic activity of DDT and its metabolites is relatively weak. This is evidenced by the fact that depending upon the dose and route of administration, and the species sensitivity of the test organism, reported studies are negative or marginally positive.

High doses of technical DDT administered orally to mice at 150 mg/kg/day for two days (acute) or 100 mg/kg DDT twice weekly for 10 weeks (chronic) showed significant increase in the number of dead implants per female. Acute treatment showed maximum sensitivity in induction of dominant lethals in week 5 and chronic treatment in week 2, with continued increases above control through week 6. Chronic, but not acute dosing, caused significant reductions in sperm viability and a reduction of cell numbers in all stages of spermatogenesis (Clark, 1974).

Oral feeding of two strains of mice at lower levels (1.05 mg/kg/day) showed little effects in reproductive response. Both CFW and BALB/C strains of Swiss mice fed DDT showed lesser parent mortality than control. Neither fertility, as measured by pairs producing young, or fecundity, as measured by litter size, was statistically different from the contol. Number of litters per pair was not diminished (Ware and Good, 1967).

Two additional studies have been reported with negative results for dominant lethality in mice (Epstein and Shaffner, 1968; Buselmaier, et al. 1972). Intraperitoneally treated male rats in doses up to 80 mg/kg for five days showed no effect in dominant lethality or fertility (Palmer, et al.

1973). Five-day oral doses of 25, 50 or 100 mg/kg given to males bred sequentially for six weeks, showed a statistically significant effect in implantation loss only in week three at 100 mg/kg level.

Oral feeding of technical DDT at 20 and 200 ppm/body weight in the diet of Sprague-Dawley rats for two generations produced no apparent effect on fertility, fecundity, neonatal morbidity or mortality through two generations (Ottoboni, 1969). By contrast, juvenile male rats of the Wistar Han strain, fed 500 mg/kg on days four and five after birth (acute) and 200 mg/kg pure DDT daily from day four to 23 (chronic) showed damaging effects on spermatogenesis: testicular weight, tubular diameter, wall thickness and number of spermatogonia (Krause, et al. 1975).

There are relatively few papers reporting the effect of DDT and metabolites on mammalian chromosomes. Johnson and Jalal (1973) studied the effect of DDT on the bone marrow of i.p. injected BALB/C mice exposed to one single administration of 100, 150, 200, 300 and 400 ppm/body weight. Doses from 150 ppm up caused a significant increase in the number of cells with fragments; sticky cells were significantly increased at all concentrations. Smaller doses were tested by Larsen and Jalal (1974) in brown and BALB/C mice: 25, 50, 100 and 250 ppm did not significantly affect the number of gaps, stickiness or mitotic indices, but deletions and gaps plus deletions were significantly higher or approached the significant levels at 50 ppm and higher concentrations.

Rats treated by i.p. or by gavage with doses ranging from 20 up to 100 ppm/body weight did not show a dose-response relationship or an increase in percent aberrations over the controls (Legator, et al. 1973).

DDE, but not DDT, caused an increase in chromosome aberrations in a Chinese hamster cell line (V79) at 30 and 35 µg/ml (Kelly-Garvert and Legator, 1973).

Palmer, et al. (1972) found a significant increase in cells with structural aberrations when an established cell line of the kangaroo rat, Potorus tridactylis apicalis was exposed to 10 µg/ml p,p' and o,p'-DDT, pp' and op'DDD and pp'DDE. The p,p'DDA was the least toxic among DDT metabolites, since only a concentration of 200 µg/ml caused a cytopathic effect, whereas DDT, DDD and DDE - p,p' and o,p'- were toxic at 20 and 50 µg/ml. Mitotic inhibition was intense in cultures treated with o,p' and p,p'DDT (40 percent and 35 percent more, respectively, than in the control). Cultures exposed to p,p' and o,p' DDD and DDE had indices of 20 to 25 percent below the control; almost no inhibition was observed with p,p'-DDA. The rate of chromosomal aberrations depended upon the isomer used: p,p'-DDT, DDD and DDE caused a two-fold increase as compared to the o,p' isomers. At 10 µg/ml p,p'-DDT, DDD and DDE caused chromosome damage to 22.4, 15.5 and 13.7 percent of the cells, respectively. Approximately 12 percent of the abnormal cells produced by p,p'-DDT and p,p'-DDE had rearrangements. Only 1/10 of the cells treated with p,p'-DDD had rearrangements. The o,p' isomers did not produce exchanges.

Mahr and Miltenburger (1976) confirmed the fact that DDA is the least effective of DDT metabolites in producing cytogenetic damage and inhibiting proliferation in the Chinese hamster cell line B14F28. The proliferation rate after a four-hour treatment was inhibited most strongly by DDD (at 75, 45 and 22 ppm), followed by DDT (81 ppm) and DDE (88 ppm); 100 ppm DDA did not produce any effect. The continuous presence of DDT (8 ppm) in the medium over three months did not result in an altered proliferation rate in cultures. Chromosome damage was observed with 41 and 81 ppm DDT, 45 and 75 ppm DDD and 44 and 88 ppm DDE. Here again DDA was the least effective in producing abnormal cells at 41, 68 and 100 ppm; at the highest concentration gaps, but not breaks, were increased. No induction of configuration anomalies was found in the experiment.

Hart, et al. (1972) found no increase in chromosomal aberrations in human or rabbit lymphocyte cultures exposed to 1, 5, 10, 30, 50 and 100 µg/ml DDT based on the analysis of 25 metaphases per level in the human cultures. Liver cells from rabbit fetuses whose mothers had been treated with DDT during pregnancy showed no difference as to chromosome damage when compared to non-treated controls.

Lessa, et al. (1976) exposed human lymphocytes _in vitro_ to very low concentrations of technical DDT ranging from 0.06 to 0.20 µg/ml and from 1 to 15 µg/ml. The lowest concentrations (0.06 to 0.20 µg/ml) are similar to those found in the plasma of individuals of the general population in Brazil. No correlation was found between DDT dose and cells with chromosomal aberrations. At 0.20, 4.05 and 8.72 µg/ml the proportion of cells with structural aberrations were significantly greater than in controls. It is interesting to note, though, that higher concentrations of approximately

12 and 15 ppm produced no such effect. Such fact may be caused by precipitation of DDT in the culture medium or may reflect a difference in the amount of binding of DDT and metabolites to the lipid moiety in the serum, or even differences in cell permeability.

Yoder, et al. (1973) reported an increase in chromatid lesions in blood cultures from a group of 42 men occupationally exposed to several pesticides, DDT included, during the spraying season, as compared with cultures made six months before when the same indiviudals had not been in contact with the pesticides for 30 days.

Rabello, et al. (1975) compared the frequency of cells with chromosomal aberrations in workers from three DDT plants, directly and indirectly exposed to DDT. There was no significant difference between these two groups. The total DDT and DDE levels in the plasma were determined. In the 25 workers in direct contact with DDT, the levels ranged from 0.16 µg/ml to 3.25 µg/ml (mean 1.03 µg/ml ± 0.79) total DDT and 0.03 to 1.77 µg/ml (mean 0.48 ± 0.52) p,p'-DDE. In these 25 indiviudals not in direct contact with the compound they ranged from 0.03 to 1.46 µg/ml (mean 0.38 µg/ml ± 0.15) total DDT and 0.01 to 0.41 µg/ml (mean 0.15 ± 0.02) p,p'-DDE. In one of the plants, though, not being in direct contact with DDT did not prevent the workers from having DDT plasma levels as high as those in workers who actually manipulated the substance. A second comparison was then made between the groups with high and low DDT plasma concentrations, which showed an increase in cells with chromatid aberrations in the highly exposed group.

When another group of eight plant workers with total DDT plasma levels ranging from 0.09 to 0.54 µg/ml (mean 0.24 µg/ml + 0.15) and DDE levels ranging from 0.02 to 0.09 µg/ml (mean 0.041 + 0.02) was compared to 10 individuals of the general population with no detectable o,p' or p,p'-DDT and DDE levels ranging from 0.02 to 0.04 µg/ml (mean 0.029 µg/ml + 0.01), no significant difference was found in the cytogenetic analysis. A positive correlation was found between DDT levels and length of exposure of all individuals, but there was no correlation between DDT levels in the plasma and frequency of cells having any type of aberrations (numerical or structural).

No effect on unscheduled DNA synthesis was seen in S-V-40 transformed human cells with concentrations up to 1000 uM DDT either with or without S-9 microsomal metabolic activation (Ahmed, et al. 1977).

In summary, the evidence in prokaryotic and fungal systems indicates that DDT and its metabolites do not produce point mutations. Although the evidence is somewhat contradictory in the dominant lethal studies, in vivo and in vitro cytogenetic studies seem to indicated that DDT is a clastogenic (chromosome breaking) substance.

Carcinogenicity

Fitzhugh and Nelson (1947) were the first to investigate the carcinogenic potential of chronic feeding of DDT in rodents. Osborne-Mandel weanling rats were fed diets containing 0, 10.0, 20.0, 40.0 and 80.0 mg/kg/day technical DDT for a period of two years. Pathologic examination revealed that the chief lesion was a moderate degree of liver damage of a characteristic type, which consisted of hypertrophy of centrolobular hepatic cells, hyalinization of the cytoplasm and focal necrosis. Although no information as to dosage or sex of the tumor-bearing animals was given, the authors concluded that definite but minimal hepatic tumor formation was evident. This conclusion was based on comparison to many hundreds of similar aged rats which spontaneously showed distinct hepatic tumors at a frequency of one percent. By contrast, of the 75 rats surviving to eighteen months, 15 exhibited either large adenomas or nodular ademonatous hyperplasia with similar microscopic morphologies, differing chiefly in size. Chronic feeding produced degenerative changes in the liver at all doses. Acute admininstration of 1000 ppm in the diet for twelve weeks produced the characteristic pathology which peprsisted for two weeks and reverted to a normal appearance when examined at weeks four, six, eight and ten post dosing.

Laug, et al. (1950) followed this study by administering lower doses of technical DDT in the diet for periods of 15 to 27 weeks to weanling rats. No hepatic cell alterations were noted in control and 1 ppm levels, with minimal effects at 5 ppm. At doses of 10 and 50 ppm, definite hepatic hypertrophy was observed, but gross alterations such as necrosis were not present. Ortega, et al. (1956) confirmed that liver alterations can be observed in rats with DDT levels as low as 5 ppm. However, this pathology was reversed to normal once the administration of the compound was stopped.

The next major report on the carcinogenicity of DDT was the work of Tarjan and Kemeny (1969) with BALB/C mice. Six generations of mice were fed either the control diet, contaminated with 0.2 to 0.4 ppm DDT, or the test diet of 2.8 to 3.0 ppm p,p'-DDT. The control group was comprised of 106 mice and the test group had 683 mice with a daily intake of 0.4 to 0.7 mg/kg. A striking increase in the incidence of leukemias was seen in the experimentally DDT treated mice, beginning at the F3 generation. Myeloid, lymphoid and aleukemias were found in 85 treated animals (12.4 percent) but only the latter two types were found in 10 controls (2.5 percent). In the F4 and F5 generations, myeloid leukemias accounted for one-third of the total. The authors further noted that in BALB/C mice spontaneous leukemia is unknown. The induction of tumors in the experimental group was significant in the F2 generation and increased almost logarithmically in successive generations from F3. A total of 196 animals (28.7 percent) versus 13 (3.2 percent) were found to have tumors in the exposed and control series, respectively. The predominant tumor type was pulmonary carcinoma (116/196 animals), and the authors claim that prior observation of their colony shows incidence of malignant pulmonary tumors to be below 0.1 percent. A variety of tumors was observed widely dispersed throughout the body and included malignant vascular tumors (22/196) and reticulosarcomas 27/196 of liver, kidney, spleen, ovary and other organs. The authors noted that these positive findings were somewhat complicated by the fact that fetal exposure via placental passage and newborn intake through breast milk may heighten adverse effects.

In a survey of 120 selected pesticides and industrial chemicals to determine their potential carcinogenicity, five pesticides, p,p'-DDT included, were among the eleven compounds that showed significant increases in tumor incidence (Innes, et al. 1969). Two hybrid strains of mice were bred by crossing C-57BL/6 with either C3HANF or AKR strains; F1 generations were designated strain X and Y, respectively. From day 7 to 28, the animals were treated by gavage, at the maximum tolerated dose of 46.4 mg/kg in a 0.5 percent gelatin suspension. From four weeks to 18 months, the chemical was mixed direct[illegible] the diet, to approximate this dose; the concentration of DDT was calculated to be 21 mg/kg/day. The frequency of mice with hepatomas in both strains as compared to controls is given in Table 6. Pulmonary tumors and lymphomas occurred in lower frequencies but are not presented in the table.

The pattern of tumor type among several experimental compounds was similar to the positive carcinogenic control compounds with the major evidence for tumorigenicity arising from the increased incidence of hepatomas. These increases were significant at the 0.01 level for the sum of both sexes and both strains, the sum of males of both strains and for the males of each separate strain of the hybrids. Although incidence of lung and lymphatic tissue tumors showed fewer increases than hepatoma, the incidence of lymphomas was significantly above negative controls for p,p'-DDT. The pulmonary tumors consisted primarily of adenomas.

TABLE 6

Frequency of Animals with Hepatomas in Two Hybrid Strains of Mice Exposed to 21.0 mg/kg/day p,p'-DDT and to a Control Diet Without DDT.

Strain	Group	Total Number of animals		Number of animals with hepatomas	
		M	F	M	F
C57 BL/6 x C3H/AmF	Exposed	18	18	11	5
	Control	79	87	22	8
C57 BL/6 x AKR	Exposed	18		7	0
	Control	90	82	5	1

In 1967, the International Agency for Research on Cancer (IARC) initiated a large investigation on the potential carcinogenicity of DDT in rodents. Studies were conducted in three different strains of mice in Lyon, France, by Tomatis, et al. (CF1); in Moscow (USSR) by Shabad, et al. (strain A); and by Terracini, et al. in Milan (Italy) with BALB/C. In addition, a study was performed on white rats in Leningrad (USSR). Although the rat study was negative, the long-term administration of DDT to mice induced a significant increase in the frequency of liver tumors, which constituted the strongest evidence to date for the possible tumorigenicity of DDT. Tomatis, et al. (1972) and Turusov, et al. (1973) fed six consecutive generations of CF1 mice technical DDT in the diet, at doses of 0.3, 1.5, 7.5 and 37.5 mg/kg/day over the lifespan. CF1 mice are characterized by a rather high incidence of spontaneous tumors mainly of the lung, haematopoietic system, bone and, in males, hepatomas. The percentage of animals bearing tumors of all types in DDT treated males (89 to 94 percent) was somewhat higher than in the male controls (78 percent). The females had similar incidence in the controls (89 percent) and in the DDT treated (85 to 90 percent). Only liver tumor incidence was clearly affected by DDT treattment. DDT treated male mice showed increases in liver hepatoma at all treatment levels, with the peak at 37.5 mg/kg/day (301/350) and similar incidence of 179/354, 181/362 and 214/383 (50 percent to 56 percent) for the three lower doses. Control males by contrast had 30 percent liver tumor frequency (97/328). In the females, no effect was seen at 0.3 and 3.0 mg/kg/day, but at the higher dose levels, tumor rates were significantly increased at 7.5/mg/kg/day (43/328) and 37.5 mg/kg/day (192/293). Liver tumors appeared earlier in the F1 through F5 generations than in the parental at higher dosages, but tumor incidence did not show consistent increases with consecutive generations as previously reported in BALB/C mice (Tarjan and Kemeny, 1969).

Comparable lifetime studies were performed by Shabad, et al. (1973) in A-strain mice. Technical DDT was given via gavage in daily dosages of 1.5 and 7.5 mg/kg/day for the parent lifetime and 10 ppm for consecutive generations, F1 through F5. DDT in 0.1 ml sunflower oil dosing began at 6 to 8 weeks of age for each generation. Strain A, which is susceptible to spontaneous lung adenomas, had an overall incidence of 7 percent in the control group. The parental generation, which received the highest dose, showed 37 percent incidence of lung adenomas. The frequencies of lung tumor formation in generations from F0 to F5 treated at 1.5 mg/kg/day were 19, 15, 24, 46, 43 and 13 percent respectively. Animals dying prior to six months in all of the control and F0 and F1 treated groups showed no tumors, whereas earlier appearance of tumors in treated F2 to F5 was seen in animals dying prior to six months. No other tumors, including liver tumors, were detected.

A third multigeneration study on mice was performed by Terracini, et al. (1973). Three dose levels of technical DDT to 0.3, 3.0 and 37.5 mg/kg/day DDT in the diet was administered to two separate colonies of BALB/C mice, beginning at four to five weeks of age, for their lifespan. The liver was the only target organ to show significant increases in the proportion of animals bearing tumors. Both males and females showed higher percentages at the 37.5 mg/kg/day level, with no excess tumorigenicity at 0.3 and 3.0 mg/kg/day. Liver tumors were present in 28/63 of the female parents and 43/58 of the first generation females, at the high dose only. Both colonies of mice showed identical results at this dosage. Incidence of malignant lymphomas was approximately 50 percent in the control, 0.3 or 3.0 mg/kg/day treated mice. At highest dosages, this incidence fell to 14 percent in one colony and 36 percent in the other. The incidence of lung adenomas was not affected by DDT treatment.

In order to determine if the liver tumors of mice would progress of regress after cessation of dosing, Tomatis, et al. (1974) treated CF-1 mice with dietary DDT of 37.5 mg/kg/day for 15 or 30 weeks. Autopsy was performed at 65, 95 and 120 weeks from the beginning of the experiment. The data indicated that a limited period of exposure to 37.5 mg/kg/day results in an increased and early appearance of hepatomas, similar to that caused by lifespan exposure. The shorter the period of exposure, the lower the incidence of liver tumors. In males treated for 15 weeks and killed at 65, 95 and 120 weeks after, the incidence of hepatomas was 13/60, 25/60 and 25/60, respectively. In males treated for 30 weeks the corresponding values were 38/60, 41/60 and 37/60, whereas the values for the controls in the same periods were 12/70, 24/83 and 33/98. In females, the incidence of hepatomas increased from the 65th to the 120th week. Those treated for 15 weeks showed 3/60, 11/60 and 5/60 after 65, 90 and 120 weeks respectively; the corresponding values for the 30-week treated were: 4/54, 11/65 and 11/54; control values were: 0/69, 0/72 and 1/90.

The size and multiplicity of the hepatomas were also correlated with the duration of exposure and time of autopsy. In this study, as in the mouse studies previously cited, the histology of the hepatomas rarely shows signs of metastases and local invasiveness.

Further confirmation of the tumorigenicity of DDT to mouse livers was reported by Walker, et al. (1972) and by Thorpe and Walker (1973) in CF-1 strains. Incidences of tumors increased from 13 percent in controls to 37 percent at 7.5 mg/kg/day and 53 percent at 15 mg/kg/day with slightly higher increases in females (control, 17 percent; 15 mg/kg/day, 76 percent). In the second study, Thorpe and Walker (1973), over 26 months, control values for both males and females were approximately 23 percent, and rose to 77 percent for males and 87 percent for females when fed 15 mg/kg/day in the diet. In contrast to the considerable shortening of lifespan seen in all previous mouse studies, minimal reduction was observed in this study.

Lifespan studies of the effect of chronic exposure to the metabolites DDE and DDD at 37.5 mg/kg/day in the diet and a mixture of 18.75 mg/kg/day each have recently been reported (Tomatis, et al. 1974). DDE showed marked effects in females CFl mice on liver tumors increasing from 1 percent (1/90) to 98 percent (54/55) in control versus treated; male incidence rose from 34 (33/98) to 74 percent (39/53). DDD showed slight increases in males only, but lung adenomas were markedly increased in both sexes. Control values for lung adenomas were 54 and 41 percent for males and females, respectively. Treatment with DDE or DDD plus DDE showed a decrease to approximately 15 percent of female mice with lung tumors. DDE reduced male incidence to 36 percent but continued treatment had no effect. The combination of DDD and DDE increased hepatoma incidence in both sexes to approximately 75 percent.

Since the most significant evidence implicating DDT as a possible carcinogen to date has been the formation of hepatic tumors in the mouse, some criticism of the use of this model with high dosages has been expressed (Deichmann, 1972). The use of animals with high spontaneous rate of tumor formation confers an added sensitivity if increases are found following exposure; the use of animal models with none or low spontaneous tumor incidences may be more indicative of actual risk.

Breslow, et al. (1974) reviewed the multigeneration studies by the IARC group to determine associations between tumor types following DDT exposure. A negative correlation was seen between lymphomas and lung, mammary, and ovarian tumors, possibly due to competing risk mortality of the diseases. Despite some spurious results caused by grouping of animals, or age specific tumor prevalence, significant associations remained. Positive association between lymphoma and bone tumor formation could be a reflection of viral factors. Viruses isolated from some tumors of CF1 mice have produced tumors in neonate mice. Hepatoma formation was less affected by lymphoma mortality. Histological examination of liver tumors in the CF1 mice showed that this hepatoblastoma is similar in morphological resemblance to human hepatoblastoma. These tumors were found in association with the ordinary type of hepatoma and isolated primarily from older animals. The hepatoblastoma proved to be more highly malignant than the hepatoma, with metastases occurring in 10 to 20 percent versus 1 to 2 percent for hepatomas. A progression from hyperplasia to neoplasia can occur spontaneously with age in mice. The phenomena of induction of hyperplasia could be attributable to age and spontaneous tumor formation, or associated with early induction by DDT activity.

One other positive report on the possible carcinogenicity of DDT in other species should be noted. Halver, et al. (1962) have observed an increase in evidence of hepatomas in rainbow trout being grown for lake stock. Following determinations of toxicity in rodents, dose fractions or multiples 1/16, 1/4, 1, 4 and 16 times were fed in a synthetic diet of caseine gellatin, minerals, etc. High doses of DDT, 2-AAF, carbon tetrachloride and other substances exhibited toxic effects. Histopathologically confirmed hepatomas appeared in the intermediate levels of DDT, DES and DMN. In a parallel study of fatty extracts from commercial ratios fed to fish, fish developed tumors also resembling mammalian hepatoma histologically.

In contrast to the positive results found in the rat, mouse and fish studies previously cited, a number of other studies have shown no significant increase in tumor formation following DDT exposure. Lifetime feeding studies with Syrian Golden Hamster at 75 and 150 mg/kg/day DDT were conducted by Agthe, et al. (1970). No increases in tumor incidences

A number of negative studies have been reported for various rat strains. Cameron and Cheng (1951) gave daily doses of 0.36, 3.6 and 36 mg/kg in oil for times up to 63 weeks. Of the characteristic lesions described by Fitzhugh and Nelson (1947) and Laug, et al. (1950), only two female rats showed the centrolobular necrosis, and no significant differences in the extent of the other pathological changes could be made between treated and untreated groups.

Two long-term feeding studies utilizing Osborne-Mendel rats have shown no significant tumorigenic response to three dosage levels of DDT. In the first (Radomski, et al. 1965), DDT was fed at 7.5 and 12 mg/kg/day in the diet for two years. At 7.5 mg/kg/day, a slight, but not significant, increase in hepatic tumor was noted; at 12 mg/kg/day no liver tumors were noted, and no differences were found between control and treated rats in tumors of other sites. In addition, DDT was fed in a mixture with 12 mg/kg/day each of aramite, methoxychlor and thiourea for 2 years, and no additive or synergistic effect for tumor formation was found.

In a similar fashion, Deichmann, et al. (1967) repeated these studies with a higher dosage of DDT - 30 mg/kg/day for 27 months. Despite the fact that the treated animals displayed increased liver weights and the characteristic liver pathology, actual tumor incidence in DDT-fed rats was less than in the control. The majority of tumors were mammary tumors in both control and treated animals. Liver tumors were found only in rats fed DDT, aramite or a mixture of these plus methoxychlor and thiourea. Mixtures of these tumorigens also had no significant effect in tumor incidence.

In order to determine the effect of diet and DDT on the development of leukemia, Kimbrough, et al. (1964) fed rats a purified high fat, purified normal fat, and normal diets with and without DDT, for varying time periods. Of the seven animals developing leukemia, four were on the high fat diet, two were on purified high fat and 35 mg/day pp'DDT, and one was on normal fat diet and DDT. No animals fed DDT and normal ratios developed leukemias. The authors concluded that chloroleukemic development in Sherman rats was a consequence of diet and unrelated to DDT treatment.

Weisburger and Weisburger (1968) fed weanling Fisher rats 10 mg DDT per day by gavage and found no liver tumors nor evident hepatotoxicity. In combination with 0.1 mg per day 2AAF, hepatoma incidence increased from 67 to 90 percent in males and 7 to 33 percent in females compared to treatment with 2AAF alone.

Rossie, et al. were able to induce non-invasive nodular liver tumors in Wistar rats by administering dietarily approximately 35 mg/kg/day of either technical DDT or sodium phenobarbital. None of the tumors were metastatic and extrahyratic tumors were slightly higher in controls than in treated animals. For DDT, liver tumor incidences of 45 percent (24 of 53 animals) were observed in treated rats while controls exhibited no liver tumors. Interestingly, sodium phenobarbital at the same dosage level showed a similar hisopathologic liver change in 44 percent (22/50) of the rats. A compilation of long-term tumorigenicity studies in rats is given in Table 7.

TABLE 7

Long Term Tumorigenicity Studies in Rats

Dose Range Mg/kg/day	Method	Strain	Duration	Results	Reference
5-40	In diet	Osborne-Mendel	2 years	Increase in liver tumors at unspecified close.	Ptizhugh and Nelson (1947)
0.36-36.0	In oil by Gavage	Osborne-Mendel	63 weeks	No effect.	Cameron and Cheng (1950)
.12-1.2	In diet	Carworth	2 years	No effect.	Traeon and Cleveland (1955)
1-2	In diet	Sherman	Variable	No increase in leukemia incidence.	Kimbrough, et al. (1964)
7.5-12	In diet	Osborne-Mendel	2 years	12 mg/kg/day. No effect. Slight increase liver tumor incidence at 7.5 mg/kg/day.	Raolomski, et al. (1965)
10	In diet	Osborne-Mendel	2.25 yrs	No effect	Deichman, et al. (1977)
30-100	In diet	Fischer	1 year	No effect.	Weissburger and Weissburger (1968)
35	In diet	Wistar	2.9 yrs	Liver tumors in 45% of animals.	Rossi, et al. (1977)
10-32	In diet	Osborne-Mendel	78 weeks	PPDDT and PPDDE - No significant tumor incidences PPDDD - Increased thyroid tumors.	NCI (1978)

In a recent published report of the National Cancer Institute (1978), bioassays of DDT, DDD and DDE were conducted in male and female Osborne-Mendel rats and B6C3F1 mice by long-term feeding. Approximately 50 animals of each sex were treated and 20 animals of each sex served as controls. The dosing period consisted of 78 weeks in which there were dosage changes during the course of the study and dosing was reported as time-weighted averages. High and low dietary concentrations of DDT were, respectively, 32.1 and 16.05 mg/kg/day for male rats, 21.0 and 10.5 for females; for DDD, males were fed 164.7 and 82.4 mg/kg/day and females 85.0 and 42.5 mg/kg/day. For DDE, males were fed 41.95 and 21.85 mg/kg/day and females 23.1 and 12.1 mg/kg/day. Increased mortality was seen in both sexes of rats dosed with DDE. No evidence of carcinogenicity was found for DDT or DDE in either sex at the given doses. DDD had no carcinogenic effects in the females but a significant increase in the low dose males of follicular cell adenomas and carcinomas of the thyroid was observed. Because of high variation of thyroid lesions in control male rats, these findings are considered only suggestive of a chemical related effect. Among dosed rats no significant increases in other neoplasms were seen as compared to controls. Administration of DDE did not result in significant incidences of liver tumors, but the compound was hepatotoxic, inducing centrolobular necrosis and fatty metamorphosis.

Time-weighted average high and low dietary concentrations of DDT for the mice were, respectively, 6.6 and 3.3 mg/kg/day for male mice, and 26.25 and 13.05 mg/kg/day for female mice; high and low average doses of DDD were 123.3 and 61.65 mg/kg/day ppm for male and female mice; average high and low doses of DDE were 39.15 mg/kg/day and 22.2 mg/kg/day for male and female mice. Significant positive associations between increased doses and greater mortality in female mice dosed with DDT and DDE were observed. Poor survival was seen in control and dosed male mice in the bioassays of DDT and DDE. The only neoplasms occurring in statistically significant increased incidence were hepatocellular carcinomas among groups receiving DDE. The incidences of these tumors in control low-dosed and high-dosed males were 0/19, 7/41 (17 percent) and 17/47 (36 percent), respectively. Corresponding figures for females were 0/19, 19/47 (40 percent), and 34/48 (71 percent).

The NCI study presented no evidence for the carcinogenicity of DDT in rats and mice, of DDD in female rats or mice of either sex, or of p,p'-DDE in rats although hepatotoxicity was evident. A possible carcinogenic effect of DDD in inducing follicular cell tumors of the thyroid of male rats was suggested. DDE was carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes (Natl. Cancer Inst.,1978).

Durham, et al. (1963) found no liver pathology in Rhesus monkeys fed 100 mg/kg/day or less for up to 7½ years. Monkeys dosed at 2500 mg/kg/day had cytoplasmic inclusions and necrosis in the liver and brain pathology. These animals died in less than six months from DDT poisoning.

There is evidence that DDT is an inhibitor of tumor takes in transplant. Mice exposed to 5.5 mg/kg/day in the diet were subjected to experimental transplantation of an ependymona. Compared to controls, treated animals were less susceptible to tumor transplantation and had increased longevity upon implantation (Laws, 1971).

In summary, the evidence for carcinogenicity of DDT in laboratory animals has been demonstrated only for the mouse in the production of liver tumors. In several other species, such as rat, monkey, and hamster, no tumorigenic effect for DDT has been shown at doses less than 50 ppm. At doses higher than that level evidence is equivocal for the rat (Fitzhugh and Nelson, 1947; Radomski, et al. 1965; Deichmann, et al. 1967; Natl. Cancer Inst., 1978).

The epidemiological studies in man to date cannot be considered conclusive in view of the small number of individuals studied. Ortelee (1958) reported on a group of 40 men with extensive and prolonged occupational exposure to DDT in manufacturing or formulating plants. An exposure rate was given to each individual based on observation on the job. The highest exposure rate was estimated to be absorbed doses of approximately 42 mg/man/day. With the exception of minor skin irritations, physical, neurological and laboratory findings were within normal ranges and no correlation between DDT exposure and frequency and distribution of the few abnormalities were seen. Laws, et al. (1967) found no evidence of adverse health effects in 35 men with 11 to 19 years of high occupational exposure (3.6 to 18 mg/man/day). No case of cancer was found.

Almeida, et al. (1975) have conducted a surveillance of workers exposed to DDT for six or more years as spray men in a malaria eradication campaign in Brazil. Although significant increases in DDT and DDE residues in the blood serum levels were observed, physical examination showed no significant increases in adverse health effects for the exposed versus control groups.

Edmundson, et al. (1969a) studied 154 individuals with occupational exposure to DDT and observed significant differences associated with race and type of occupation. Nonwhite formulators and agricultural sprayers showed greatly elevated serum concentrations but during the two-year time of study no clinical effects related to DDT exposure were observed.

Hayes, et al. (1971) administered doses up to 35 mg/man/day to volunteers for 21.5 months. Liver function studies of SGOT, plasma cholinesterase, and BSP retention exhibited no significant change from normal for these volunteers. A number of other health parameters were studied and no definite chemical or laboratory evidence of injury by DDT was found at the prevailing levels of intake. This led the authors to conclude that DDT had a considerable degree of safety for the general population.

Several authors have examined the storage of DDT in persons with various diseases. Maier-Bode (1960) found no differences in storage of DDT or DDE in 21 persons who died of cancer and 39 others who died of other diseases.

The difficulty in making these kinds of associations is illustrated by the results of Radomski, et al. (1968). Pesticide concentrations were determined in fat and liver at autopsy for 271 patients previously exhibiting various pathology of liver, brain and other tissues. Another group that had previously had infectious diseases was examined. High significant elevations of DDT and DDE were found in carcinomas of varying tissues. Fat concentrations of DDE, DDT, DDD and dieldrin were consistently elevated in cases of hypertension. These observations were clouded by the great individual variability of pesticide levels regardless of the disease category.

Two further studies (Hoffman, et al. 1967; Cassarett, et al. 1968) have been conducted on the levels of DDT in tissues of patients with cancer and other chronic diseases. One showed higher DDT residues in cancer patients (Cassarett, et al. 1968). No conclusions can be made from these studies as to a possible causal relationship.

Sanchez-Medal, et al. (1963) noted 20 cases of aplastic anemia over an eight-year period in a Mexico City Hospital. In 16 out of 20 cases, the patients had repeated contact with pesticides during the prior six months. Insecticides implicated were DDT alone or DDT in association with lindane, dieldrin or DDVP. One 13-year old boy had been exposed repeatedly to DDT alone for two years and exposure was intensified to every other day in the prior four months. He was accidentally exposed to 10 percent DDT spray in the hospital and died thirty hours later due to a worsening blood discrasia. The American Medical Association Registry on Blood Discrasia reported 44 cases of aplastic anemia associated with pesticide exposure through 1963. Of these cases, 19 were related to DDT and in three DDT was the sole agent (Erslev, 1964).

At the present time, no evidence of neoplasia has been found in the studies performed in occupationally exposed or dosed volunteer subjects. Medical histories have been essentially normal. However, these studies do not constitute an adequate basis to make conclusions regarding human carcinogenicity because of small sample size and short duration in terms of average human life-span.

CRITERION FORMULATION

Existing Guidelines and Standards

In 1958, U.S. Department of Agriculture began to phase out the use of DDT in insect control programs. Spraying was reduced from 4.9 million acres in 1957 to just over 100,000 acres in 1967, and DDT was used as a persistent pesticide thereafter only in the absence of an effective alternative. In 1964, the Secretary of Interior issued a directive that use of chlorinated hydrocarbons should be avoided in interior lands. This was extended in 1970, when 16 pesticides, including DDT, were completely banned for use on Department of Interior lands. By 1969, DDT registration and usage was curtailed by the USDA in various areas of the cooperative Federal State pest control program. In November 1969, the USDA announced its intention to discontinue all uses of DDT non-essential to human health and for which there were safe and effective substitutes. In 1970, a major cancellation of Federal registrations of DDT products by the USDA on 50 food crops, domestic animals, finished wood and lumber products, and use around commercial, institutional, and industrial establishments was completed.

Major responsibility for Federal regulation of pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (1947) was transferred to the U.S. EPA. In January, 1971, U.S. EPA issued notices of intent to cancel all remaining Federal registrations of products containing DDT. A hearing on the cancellation of Federal registration of products containing DDT was held beginning in August, 1971 and concluding in March, 1972. The principal parties to the hearing were 31 DDT formulating companies, the USDA, the Environmental Defense Fund, and the U.S. EPA. This hearing and other evidence from four Government reports including the December 1969 Mrak Commission Report were instrumental in the final cancellation of all remaining crop usages of DDT in the U.S., effective December 31, 1972. During the same period (October 1972), a Federal Environmental Pesticide Control Act (FEPCA) was enacted which provided EPA with more effective pesticide regulation mechanisms. The cancellation order was appealed by the pesticides industry in several U.S. courts. On December 13, 1973, the U.S. Court of Appeals for the District of Columbia ruled there was substantial evidence in the record to support the U.S. EPA ban on DDT. In April 1973 the U.S. EPA, in accordance with authority granted by FEPCA, required that all products containing DDT be registered with the Agency by June 10, 1973. Since that time, the U.S. EPA has granted requests to the states of Washington and Idaho and to the Forest Services to use DDT on the basis of economic emergency and no effective alternative to DDT being available.

Authority to regulate hazards arising from the manufacturing and formulation of pesticides and other chemicals resides with the Occupational Safety and Health Administration (OSHA). Under the terms of the Occupational Safety and Health Act of 1970, the National Institute of Occupational Safety and Health has been responsible for setting guidelines, criteria, and standards for occupational exposure. The OSHA exposure limit for DDT on skin has been set a 1.0 mg/m^2. Further, DDT has been classified as a suspected occupational carcinogen that should be cautiously handled in the workplace.

The decision to ban DDT was extensively reviewed relative to scientific and economic aspects in 1975 (U.S. EPA, 1975). No new evidence was found contradicting the original finding of the Administrator in 1972.

Year	Agency Org.	Standard	Remarks
1971	WHO	0.005 mg/kg body weight	Maximum Acceptable Daily Intake in food
1976	U.S. EPA	0.001 µg/l	Quality Criteria for Water
1977	Natl. Acad. Sci., Natl. Res. Counc.	-	In light of carcinogenic risk projection, suggested strict criteria for DDT and DDE in drinking water
1978	Occup. Safety Health Admin.	1 mg/m^2	Skin exposure
1978	U.S. EPA	0.41 µg/l 0.00023 µg/l	Final acute and chronic values for water quality criteria for protection of acquatic life (fresh water)

Current Levels of Exposure

Most of the reported DDT concentrations in air are associated with high usage of DDT prior to 1972. Stanley, et al. (1971) analyzed air samples from nine localities. DDT levels ranged from 0.1 ng/m.^{3} to 20 ng/m^3. Air samples collected in July 1970 had 0.00007 ng/m^3 (Prospero and Seba, 1972) over the Atlantic Ocean. The actual levels of DDT in the ambient air at the present time are difficult to estimate but are probably at the lowest ranges of Stanley's estimates. The significance of pesticide levels in the air have been carefully reviewed and the consensus is that the levels of DDT found in the ambient air are far below levels that might add significantly to the total human intake (Spencer, 1975).

Kenaga (1972) gave the following relative values for residues for DDT and its metabolites found in various types of waters: rain water, 0.2 µg/l; fresh water, 0.02 µg/l; sea water, 0.001 µg/l. Assuming average daily intake of water to be 2 liters in any given year, maximal DDT intake from water would be 0.007 mg. This figure is equivalent to the estimated dietary intake of DDT in a single day for a 19-year-old male (U.S. EPA, 1975). Therefore, it is concluded that DDT intake from potable water does not contribute significantly to the overall exposure.

Duggan and Corneliussen (1972) calculated the average daily intake of total DDT residues in 1965 as 0.0009 mg/kg and decreasing to 0.0004 mg/kg in 1970. Market basket studies have shown significant declines between 1970 and 1973 of DDT and DDD residues of 86 and 89 percent, respectively. DDE decreased by 25 percent over this period of time. Dairy, meat, fish and poultry constitute 95 percent of the total ingested DDT sources with dairy products contributing 30 percent of this amount. Average human fat storage for the time period of 1970 to 1973 has decreased from approximately 8 ppm to 6 ppm in the U.S. population. Based on these declines and the most current figures of of 1973 for intakes it is estimated that current levels of dietary intake are approximately 0.0001 mg/kg/day with DDE comprising over 80 percent of this amount. Assuming the average male weighs 70 kg the average daily intake would be 0.007 mg/day or 2.56 mg/year.

Human exposure to DDT is primarily by ingestion of contaminated food. Air and water intake is negligible and amounts to probably less than 0.01 mg/year. Therefore, by our estimate, total intake of DDT per year for the average U.S. resident will be less than 3 mg/year.

Special Groups at Risk

The entire population of the U.S. has some low level exposure to dietary contaminants. Minimal exposure from air and water sources, however, may be more important in previously heavily sprayed agricultural areas, where large amounts of residues may still be present.

In 1975, estimated DDT production was 30 to 49 million pounds (Natl. Inst. Occup. Safety Health, 1978). The primary producer of DDT in the U.S. is the Montrose Chemical Co. It is assumed that there are other companies involved in the formulation of their products with DDT, but no data are available.

Groups at special risk are workmen in manufacturing plants and formulating plants and applicators, handlers and sprayers.

During such times as exceptions are granted by the U.S. EPA for crop usage or during use for public health measures, those involved in handling or applying DDT may have considerable exposure.

Estimating the number of indiviuduals at high risk due to occupational exposure is difficult. It is estimated that 8700 workers are involved in formulating or manufacturing all pesticides. Since DDT constitutes much less than 10 percent of the total, the maximal number of exposed workers would be approximately 500. Since usage of DDT is severely limited, persons exposed by application would probably be fewer.

Basis and Derivation of Criterion

Since no epidemiological evidence for the carcinogenicity of DDT in man has been reported, the results of animal carcinogenicity studies conducted by feeding DDT or its metabolites over the lifespan of the animal are regarded as the most pertinent data. Although a number of studies have been reported for various species, the major evidence for the tumorigenicity of DDT is its ability to induce liver tumors in mice.

Under the Consent Decree in NRDC vs. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." DDT is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of DDT in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of DDT corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish (2)		0.0098 ng/l	0.098 ng/l	0.98 ng/l
Consumption of fish and shellfish only.		0.0098 ng/l	0.098 ng/l	0.98 ng/l

(1) Calculated by applying a modified "one hit" extrapolation model described in the FR 15926, 1979, to the animal bioassay data presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Greater than 99 percent of the DDT exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 39,000 fold. The remaining less than one percent of DDT exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of DDT (1) occurring from the consumption of both drinking water and aquatic life grown in water containing the corresponding DDT concentrations and, (2) occurring solely from the consumption of aquatic life grown in the waters containing the corresponding DDT concentrations. Although total exposure information for DDT is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into the ambient water quality criteria formulation because of the tenuous estimates. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

The case of DDT and its possible role as a human carcinogen is complicated by several factors. Despite widespread use and exposure over thirty years, no positive associations with human cancer have been found to date, although the number of individuals studied is not statistically large. It is a chemical with high efficacy and has been extremely effective all over the world for public health measures. However, its slow biodegradability and propensity to accumulate in nontarget species have made it particularly hazardous for many fish and bird species. For mammals, however, it has a low acute toxicity as compared to other alternate pesticides.

DDT has not been shown to produce point mutations or teratogenic effects in a wide battery of tests. Some evidence for its clastogenic properties, however, make it suspect.

The primary evidence for the carcinogenicity of DDT and metabolites to date has been the induction of liver tumors in mice. Studies in other species have consistently shown little or no effect and in the mice only liver tumors have shown an increase. The evidence for the carcinogenicity of DDT would be much more convincing if other species or sites of tumorigenic action could be conclusively demonstrated. This is in light of the fact that DDT has been probably the most extensively studied compound in modern science.

Current levels of exposure would seem to pose extremely small risk to persons in the U.S. DDT and DDE are preferentially stored in fatty compartments that are not actively dividing and subject to carcinogenic changes.

The use of DDT has been restricted in several countries because of its impact on the environment and its tumorigenic effect in mice. This is a reasonable proposition based on numerous reports. Therefore, the levels proposed in this document should ensure the health of wildlife and the co-existing human population.

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APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of DDT*

DDT is a synthetic, chlorinated hydrocarbon insecticide which has broad-spectrum insecticidal activity. DDT residues have been detected in a wide variety of fruits, vegetables, meat, fish and poultry, and will probably continue to be present in agricultural produce indefinitely as a consequence of the persistence of DDT in soil. DDT is absorbed completely after inhalation and ingestion and absorbed poorly through skin. DDT has not been found to be mutagenic in bacterial test systems, either with or without metabolic activation. The evidence from mammalian test systems *in vitro* and *in vivo* is inconclusive.

There is no epidemiological evidence relating to the carcinogenicity of DDT, but there are a number of carcinogenicity studies conducted by feeding DDT to animals. A number of chronic studies have been reported in various species, but the major evidences for tumorigenicity in mice and rats are described below. In mice, DDT increased tumor incidence significantly in experimental groups as compared to controls in liver (Innes, et al. 1969; Walker, et al. 1972; Turusov, et al. 1973; Terracini, et al. 1973; Thorpe and Walker, 1973), lungs (Tarjan and Kemeny, 1969; Shabad, et al. 1963) and lymphoreticular tissue tumors (Innes, et al. 1969 and Tarjan and Kemeny, 1969). In rats, liver tumors were significantly increased in the experimental group as compared to controls in two studies (Fitzhugh and Nelson, 1947; Rossi, et al. 1977).

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*This summary has been prepared and approved by the Carcinogens Assessment Group of EPA on July 25, 1979.

The negative NCI mouse study might be explained on the basis of shorter duration of exposure, low dose in male mice, and the use of a strain different from the other positive studies. The negative NCI rat study might be explained on the basis of shorter duration of exposure and lower dose compared to that used in the Fitzhugh study. There are other negative carcinogenicity studies in mice, rats, hamsters, dogs, and monkeys.

The water quality criterion for DDT is based on a comparison of the cancer rates in Israel, where DDT exposure has been high for an extended period of time, and the United States (Tursov, et al. 1973). It concluded that if water alone is consumed, the water concentration should be less than 0.36 micrograms per liter in order to keep the lifetime cancer risk below 10^{-5}. If fish and water are consumed, the water concentration should be less than 0.98 nanograms per liter to achieve the same risk level.

Summary of Pertinent Data

The water quality criterion for DDT can be derived on the basis of two independent sets of data, neither of which is completely satisfactory. The first method is based on the most sensitive animal chronic bioassay available, which is the six-generation study by Turusov, et al. (Jour. Nat. Cancer Inst., 1973) in CF-1 mice. The second method is based on a comparison of the lifetime incidence of nervous system cancer cases between residents of New York State (except New York City) and residents of Israel who were born in Europe or America.

The first method results in water quality concentrations so low that over 95 percent of surface water in the U.S. would fail to meet the criteria. This method also implies that the lifetime risk from current ambient concentrations is approximately three percent, which seems unrealistically high for DDT exposure alone in view of the absence of reported carcinogenic effects in heavily exposed populations. The second method is based on extremely tenous assumptions, but it does use human data to put an upper limit on the carcinogenic effectiveness of DDT.

METHOD 1

In the Turusov mouse study, the six generations of the lowest dose group (2 ppm) of males had 179 animals with hepatomas out of 354 animals analyzed, whereas in controls 97 out of 328 animals had hepatomas. The data used for the criterion are:

$n_t = 179$

$N_t = 354$

$n_c = 97$

$N_c = 328$

$Le = 104$ weeks

$le = 104$ weeks

$d = 2 \times 0.13 = 0.26$ mg/kg/day

$w = 0.030$ kg

$L = 104$ weeks

$R = 39{,}000$

$F = 0.0187$ kg/day

With these values the slope parameter is $B_H = 18.055$ $(\text{mg/kg/day})^{-1}$. The result of the calculation is that if fish and water are consumed the water concentration should be less than 0.053 ng/l in order to keep the individual lifetime risk below 10^{-5}. If only water were consumed $(F = 0)$ the corresponding concentration is 20 ng/l.

METHOD 2

There is strong evidence that method 1 overstates the DDT risk, either because the animal experiments overstate the human risk or because most people do not eat fish contaminated to the extent assumed in the model. The basis for stating this is that countries like Israel where the levels of DDT exposure have been high and widespread have experienced no excess cancer incidence as compared to the United States. As an upper limit estimate of cancer risk from DDT exposure, we can make the unsupported assumption that DDT does cause human cancer with some probability which is proportional to the lifetime exposure and we can make the _reductio ad absurdum_ argument that cancer incidence in the organ site where the largest excess in incidence occurs in Israel is due solely to DDT, which of course is not true. Taking the nervous system as a reasonable candidate site for the action of DDT, we can make the following estimate which is intended only to put upper bounds on the carcinogenic effectiveness of DDT.

The high exposure in Israel is reflected in the higher fat levels measured by Wasserman, et al. According to their data the average level in Israel is 16.33 ppm (based on three studies), whereas in the United States it is 9.04 ppm (based on ten studies). Using the following relationship, developed by Hayes, et al. and Durham, et al. between the daily dose I(mg/day), and the concentration, C (ppm) in body fat:

$$\log I = (1/0.7)(\log C - 1.3),$$

the difference in the average daily doses between in Israel and the United States was calculated to be 0.751 - 0.323 = 0.428 mg/day. The lifetime incidence of cancer for Israel and New York State is tabulated below from Table 8.3.

	Lifetime Incidence (percent)	
Population (males)	Nervous System	All Sites
New York State	0.5	28.8
Israel:		
All Jews	1.1	24.9
Born Israel	1.3	21.4
Born Europe or America	1.1	24.1
Born Africa or Asia	0.7	18.6
Non - Jews	0.5	15.3

Relative to New York, the excess lifetime risk of nervous system cancer in migrants to Israel from Europe and America is 1.1 - 0.5 = 0.6 percent. This is caused by an excess intake of 0.428 mg/day. Therefore, the intake I resulting in 10^{-5} risk is

$$I = (10^{-5}/0.006) \times 0.428 = 7.13 \times 10^{-4} \text{ mg/day}$$

If this intake comes from fish and water, the concentration of water would be:

$$C = 7.13 \times 10^{-4}/(2 + 39{,}000 \times 0.0187)$$
$$= 0.98 \text{ ng/l}$$

If the intake comes from water alone, the concentration would be:

$$C = \frac{7.13 \times 10^{-4}}{2} = 0.357 \text{ ug/l}$$

Therefore, according to method 2, if fish and water are consumed, the water concentration should be less than 0.98 ng/l in order to keep the individual lifetime risk below 10^{-5}. If only water is consumed, the corresponding concentration is 0.36 ug/l. The equivalent slope factor for method 2 is:

$$B_H = \frac{70 \times 10^{-5}}{2 \times 3.57 \times 10^{-4}} = 0.98 \text{ (mg/kg/day)}^{-1}$$

Method 2 is recommended because it gives some basis for avoiding the unrealistically low concentrations imposed by considering only the animal data.

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